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RELATIONSHIP OF NOXIOUS GASES TO CARCINOMA OF THE LUNG IN RAILROAD WORKERS

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The medical records of 6,506 deaths among railroad workers included 818 deaths from malignant disease of various organs, and 154 of the deaths were ascribed to primary carcinoma of the lung and/or bronchus. The 154 deaths were classified according to the amount of exposure to exhaust fumes from diesel engines involved in the decedent's actual day's work. The group of workers regularly exposed to diesel exhaust, especially engineers and firemen, proved not to have any higher rate of bronchopulmonary carcinoma than did the nonoperating groups, which included clerks and janitors. Paradoxically, the highest rate was in the clerical group, which also contained a higher percentage of urban as distinguished from rural residents. The place of residence was more significant than the type of work. The cases of bronchopulmonary carcinoma here studied all occurred in men even though about 4% of the employees in the department concerned were women.

THIS study is presented in order to compare primary lung cancer deaths in railroad workers with those in the "non-railroader" public. It analyzes the lung cancer rate of the railroad employees from the standpoint of occupational exposures to noxious gases and air pollutants.

Lung Cancer as an Occupational Hazard

Lung cancer has been recognized for many years as an occupational hazard. The earliest reported case, related to radioactive substances, was in 1879.[1] Farber,[2] in his book "Lung Cancer," said that, in 1935, Lange found that between 60 and 70% of all miners at Schneeberg (Saxony) died of bronchogenic carcinoma due to exposure to pitchblende in the ore. Heuper,[1] head of the environmental section of the National Cancer Institute, mentioned that the total number of Schneeberg miners who died from cancer of the lung between 1879 and 1939 was approximately 400, while the number of Joachimsthal (Czechoslovakia) miners who fell victim to this disease reached 225 between 1926 and 1943. Machle and Gregorius [3] stated that, of 193 deaths in chromate workers, 66 were from cancer, mostly of the lungs. In addition to the uranium and chromate listed above, arsenic, nickel, asbestos, coal tar fumes, and beryllium have from time to time been suspected as lung carcinogens. Today, environmental and experimental studies are being conducted to ascertain the possible role of air pollution by noxious fumes as a carcinogenic factor in the production of lung cancer in human beings.

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Mortality from cancer of the respiratory system in men in 1956 (20%) was four times as high as in 1930 (5%). Mancuso [4] attributed this rising trend in lung cancer to three factors: (1) tobacco smoking; (2) occupational exposure to carcinogens; and (3) atmospheric pollution. He stated that opinions as to the degree of importance to be attached to each of these factors vary among members of the medical and research professions.

Heuper [1] reported that "three-fourths of the cases of lung cancer in railroad employees occurred among the operating group of workers—a group which represented only 25% of the total number of said employees." The only other related statistical study found in the literature was that of Raffle,[5] who, in 1956, recorded 11 cases of lung carcinoma in London railroad workers during the period 1950 to 1954. He concluded that those deaths did not have any apparent causative relationship to diesel fume inhalation.

Incentive for this statistical study dates from Jan. 8, 1959, when a legal suit was instituted against the Pennsylvania Railroad by one of its disabled machinists, who alleged he had developed cancer of the lung as a result of inhaling diesel shop fumes between 1953 and 1956. From the medicolegal standpoint, this case—which, incidentally, was won by the railroad—indicated a growing belief that inhalation of diesel fume exhausts might be a cause of primary lung cancer.

Source of Material for Study

In view of the paucity of medical information regarding lung cancer in railway workers, the medical records of the Baltimore and Ohio Railroad relief department were used for accurate, unbiased, standardized evaluation. Its employee membership and mortality records for the period from Jan. 1, 1953, to Dec. 31, 1958, were assiduously reviewed and tabulated. Comparisons were made with deaths from all causes and deaths from lung cancer of the nonrailroader public. Statistics were then collated to determine any possible relationship between incidence of lung cancer in various employee groups and their occupational exposure to the noxious fumes.

A total of 6,506 causes of death were reviewed—including 818 deaths from malignancies of the various body organs. All certified transcripts of deaths from malignancies were then inspected. A total of 154 deaths were found to be due to primary carcinoma of the lung and/or bronchus. The causes of these deaths were of significance because a majority of the dead employees had spent the greater portion of their working years at the same position, in engine, train, shop, or clerical service.

Grouping of Railroad Workers

Railroad workers are arbitrarily divided into two different classifications, i. e., the operating and nonoperating groups. However, for the purpose of this study, because they were exposed to varying amounts of noxious fumes in their different occupations, they have been divided into the following three groups:

Group 1 (Operating).—Group 1 employees are directly exposed to exhaust fumes from diesel engines (oil) or steam engines (coal) during operation of trains, locomotives, motors, cars, and all other rolling vehicles. This group is composed of engineers, firemen, motormen, hostlers, road brakemen, yard helpers, yard foremen, conductors, switchmen, yardmasters, and trainmasters.

Group 2 (Nonoperating).—Group 2 includes those members who perform mechanical services or manual labor in either shops or roundhouses. They are exposed, to a lesser degree, to air pollutants from diesel oil, coal smoke, soots, dusts, lubricating oils, and welding fumes. Those included in this group are carmen, carmen helpers, electricians, machinists, boilermakers, blacksmiths, crane operators, stationary engineers, pipefitters, molders, painters, welders, carpenters, crossing watchmen, fireknockers, trackmen, patrolmen, and dump operators.

Group 3 (Nonoperating).—Group 3 employees are rarely occupationally exposed to noxious fumes during the course of their railroad work. This group is comprised of clerks, laborers, janitors, agents, bridge inspectors, and port captains.

The Diesel Engine and Its Exhaust By-Products

Although for many years railroad workers have been exposed to noxious fumes from steam engine (coal) exhaust and various air pollutants in shops, emphasis is now on diesel oil exhaust as a possible carcinogenic factor. The Baltimore and Ohio Railroad initiated its dieselization of locomotives in 1935 and the program was 100% completed in 1958.

The diesel engine was invented in 1892 by Dr. Rudolph Diesel, a German scientist. The first diesel engine–powered locomotive for underground mines was placed in service in the Ruhr coal mining district of Germany in 1927. The diesel engine burns diesel fuel or "fuel oil," which is a hydrocarbon mixture consisting generally of about 85% carbon. Combustion by-products [6] are carbon dioxide, carbon monoxide, sulfur dioxide, nitrogen oxide, and aldehydes (formaldehyde, acetaldehyde, pyruvic aldehyde). In addition to these exhaust products of diesel fumes, the following aromatic polycyclic hydrocarbons have been identified: pyrene, fluoranthene, chrysene, fluorene, 1:2 benzpyrene, 3:4 benzpyrene, and 1:12 benzperylene. Carbon monoxide, nitrogen oxide, and aldehydes, which can be toxic in unusual concentrations, are recognized to be noncarcinogenic.

Straub,[7] general claims attorney for the Chesapeake and Ohio Railroad, in 1955 concluded that "in the normal course of railroading, there are only remote possibilities of encountering atmospheres which, together with the time factor, likely will result in harmful effects."

The California Public Utilities Commission [8] in 1956 received a report from the Advisory Committee of the Association of American Railroads on the question of possible hazards to operating crews resulting from exposures to exhaust fumes from diesel locomotive engines. One thousand medical examinations were completed, and "there appeared to be no significant amount of acute health damage and no different experience of those riding in the head engine and the caboose of the freight trains from either the combustion products of diesel locomotives or from the dusts arising out of the use of track sanders."

Kotin and colleagues [9] stated that in a well-operated diesel engine only slight traces of polycyclic hydrocarbons were produced, but by "fuel injection interference" their concentration was increased very considerably and 3:4 benzpyrene appeared. They also mentioned that 3:4 benzpyrene experimentally produced skin papillomas in black mice and skin cancer in strain A mice.

Donovan and co-workers [10] made a survey of the exhaust constituents from a well-maintained diesel engine and found quantities of fluorene, pyrene, and fluoranthene but no 3:4 benzpyrene.

Bailey and colleagues,[6] in their 1959 investigation into the composition of diesel engine exhausts, made this observation: "Most authoritative reports suggest that the contribution of the correctly operated diesel engine is almost insignificant, as far as major harmful pollutants are concerned." They concluded that the principal variable which influences 3:4 benzpyrene production is the fuel flow to the engine and that the exhaust is free of benzpyrene as long as fuel delivery to the engine does not exceed the maker's recommended figure by more than 100%.

Chambers,[11] director of air pollution research, Los Angeles, made the following statement: "All types of vehicles (automobiles and other petroleum-fueled vehicles, except electric-powered) contribute their proportionate share of emissions, but, in most localities, the enormous preponderance of gasoline-driven machines makes the relatively small contribution of diesel, gas, and coal-propelled units quite insignificant, except in the immediate vicinity of their exhaust vents."

Statistical Results and Their Interpretations

In connection with the incidence of primary lung cancer in members of the relief department of the Baltimore and Ohio Railroad between Jan. 1, 1953, and Dec. 31, 1958, the table shows the exposures in each year, with the actual and expected death rate per 100,000.

The method of standardizing the natural death rates for men was as follows:

1. The average relief department membership for each year was determined, and it was then broken into five-year age groups to coincide with the same age groups used by the American Cancer Society.

2. The number in each age group in each year was then multiplied by the death rate per 100,000 reported by the American Cancer Society for the general population for the corresponding age group in the year being calculated and this gave the number of expected deaths.

3. The 154 lung cancer deaths under consideration were likewise distributed by years in five-year age groups, and this produced the actual number of deaths in each year.

4. The total number of the expected and actual deaths, as determined above, was then divided by the exposures (average memberships in each year) to determine the expected and actual death rates for each year.

5. The total number of actual and expected deaths during the six years was then obtained and divided by the total exposures for the six years, thus resulting in the expected and actual death rates for that period.

The larger proportion of deaths from lung cancer occurred in group 3 (clerical), with 89.4% of the expected deaths. Second was group 1 (engine and train service), with 87.5% of the expected deaths. The lowest number of deaths, group 2 (shop), had

*Expected and Actual Number of Deaths from Lung Cancer, 1953-1958**

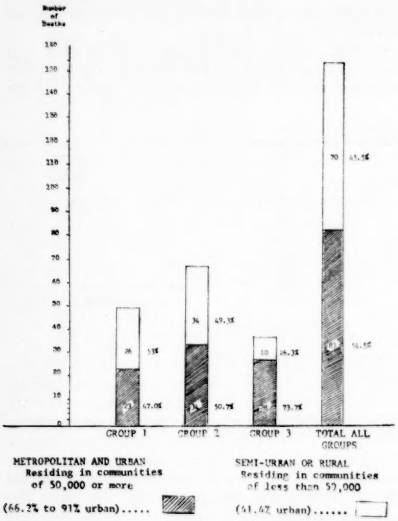
	Group 1			Group 2			Group 3			Total All Groups		
		Deaths			Deaths			Deaths			Deaths	
Yr.	Av. No. of Members	Expected	Actual	Av. No. of Members	Expected	Actual	Av. No. of Members	Expected	Actual	Av. No. of Members	Expected	Actual
1953.....	13,210	8.209	8	22,930	13.635	12	7,680	6.458	3	43,820	28.302	23
1954.....	12,300	8.566	6	21,350	14.263	14	7,260	6.688	9	40,970	29.517	29
1955.....	12,160	8.870	3	20,380	15.012	11	6,890	6.921	4	39,430	30.803	18
1956.....	12,470	9.860	8	19,820	16.629	11	6,660	7.301	10	38,950	33.790	29
1957†.....	12,250	10.322	13	18,790	17.183	8	6,410	7.521	7	37,450	35.026	28
1958†.....	11,940	10.150	11	17,290	16.807	11	5,950	7.635	5	34,490	34.592	27
6-yr. total	73,790	55.977	49	120,470	93.529	67	40,850	42.524	38	235,110	192.030	154
% of actual to expected death rate per 100,000		87.5			71.6			89.4			80.2	
National rate per 100,000		75.9			77.6			104.1			81.7	
Relief dept. rate per 100,000		66.4			55.6			98.0			65.5	

* Based on standardized national death rates and annual relief department exposures for each occupational group.
† Estimated national death rates furnished by American Cancer Society.

71.6%. However, the total of all groups indicated only 80.2% expected deaths, rather than 100%, the national expectancy (basis for standardization).

Comparison of the expected total national death rate of 192 with the actual rate of 154 deaths of Baltimore and Ohio employees implies that fewer employees of the Baltimore and Ohio Railroad died from lung cancer than did a comparable group of the general public. In addition, the number of deaths in group 1, the group with the maximum occupational exposure to noxious fumes, again is less than the norm or expected.

Among our workers, the percentage of deaths from lung cancer in the operating group was not disproportionate to those deaths in the nonoperating group. Percentage of members in group 1 (operating group) was 31.4 and in groups 2 and 3 (nonoperating groups) 68.6; percentage of deaths from lung cancer in group 1 was 31.8 and in groups 2 and 3, 68.2. This is in contrast to the figures of Heuper,[1] which indicated that three-fourths of the deaths from lung cancer occurred among the operating group of workers, and this represented only 25% of the total number of said employees.



Residential study of various groups in relation to urban and rural locations.

Significance of Statistics

Careful review of the table and the figure in this paper indicates that the results of the statistical studies are of definite significance. This is especially true for group 2 (shop) workers, who had the lowest percentage of lung cancer deaths (71.6%). In an attempt to discover an explanation for these findings, a study was made of the predeath residences of the 154 employees, and the results are expressed in the figure. It shows almost 50% distribution of the members of group 2 for both urban and rural residences. However, of greater importance is the observation of members in group 3 (clerical), for it indicates that 73.7% of the members reside in urban areas. This may possibly be a factor in explaining the higher percentage of lung cancer in clerks, as compared to other employees.

Of further interest is the realization that all 154 deaths from lung cancer occurred in men, despite the fact that about 4% of the employees of the relief department during that period were women. The majority of women workers in the railroad industry perform clerical duties and, since no deaths from cancer in women are found in this study, it suggests that, if all the women members of the relief department during the years 1953 to 1958, inclusive, were removed from the study, group 3 (clerical) would show an even higher percentage of lung cancer.

Finally, it was noted that the average age at death from lung cancer in our workers was 65.1, with 55% of the deaths occurring after the retirement age of 65 years. Apparently their longevity was not affected by the exposure to noxious fumes, since the ages at death in groups 1, 2, and 3 were about the same. However, there was a marked difference between the ages of our decedents from cancer of the lung, as compared to the ages at death of our employees from all causes, since the average for the latter group over the same six-year period was 70.13.

Conclusions

Our statistical studies fail to reveal any relation between noxious fumes associated with railroad work and primary lung carcinoma. Ordinarily, one would assume that constant exposure to noxious fumes would produce an increase in lung cancer, but this report did not substantiate this hypothesis. Actually, according to mortality records of the Baltimore and Ohio Railroad relief department, for the six-year period, 1953 to 1958, inclusive, the percentage of deaths from cancer in male employees attributable to primary lung cancer (80%) was actually 20% lower than the expected national percentage (100%).

Evaluation indicates the inconsistencies associated with exposure to these noxious fumes. Most deaths from lung cancer were reported in the clerical group of employees, who actually had practically no occupational exposure to the fumes. Paradoxically, those members with the greater exposure to the fumes, namely groups 1 and 2, had less lung cancer than the clerical group.

The study supports the general contention that carcinoma of the lung predominantly affects the male sex, since all 154 cases were in men. Average age at death from carcinoma of the lung was 65.1 years, with 55.2% of the deaths occurring after the age of 65 (retirement age). Carcinoma of the lung

among our railroad workers in 1958 showed a continued annual increase, thus paralleling the national trend.

Our records reveal that there is no higher percentage of lung cancer in members of the operating group of railroad employees than in the nonoperating groups, which have lesser exposure to noxious fumes. Railroad workers live predominantly in metropolitan and urban areas (54.5%), compared with rural residences (45.5%). The difference in the two locations is created by the clerical group of employees, 73.7% of whom live in urban areas. This is the group which has the highest percentage of lung cancer in all of our workers.

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CHANGING TRENDS IN CLINICAL INVESTIGATION

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Changing trends in American medicine, medical education, and research have for many years been favorite subjects for messages from chairmen. Nevertheless, since this represents the Centennial Meeting of the Section on Experimental Medicine and Therapeutics, it seems timely to discuss briefly a few of the problems related to the dynamic developments in science in terms of their impact on clinical investigation.

The word "clinical" is derived from the Greek word *klinikos* which means bed; hence, Dr. Fuller Albright pointed out 15 years ago: "Since animals do not sleep in beds, it is quite clear that 'clinical investigation' has primarily to do with the investigation of sick people and is concerned only secondarily, if at all, with sick laboratory animals."[1] One could argue the restrictions imposed by the above statement. Few would disagree that the greatest contributions from clinical investigation have come from success in opening up new knowledge of mechanisms, diagnosis, and treatment of disease in human beings.

Opportunities in clinical research are greater than ever before. Money is relatively plentiful; new institutions have been developed, and the old ones have increased in size. There are many indications that there will be more opportunities for capable men in the future. Yet these developments have created a series of problems which all who are concerned with the vital responsibility of fostering and maintaining productive clinical research must face. Clearly, the primary responsibility will continue to be that of stimulating and recruiting to clinical investigation men with fertile minds who are motivated for research. However, there is little question that recruitment of such men to clinical medicine will increasingly involve competition with many other fields of science.

The astonishing advances in all of the physical and natural sciences have created a peculiarly difficult dilemma for the clinical investigator. He recognizes the unassailable fact that progress in clinical medicine has resulted almost without ex-

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Chairman's address, read before the Section on Experimental Medicine and Therapeutics at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 9, 1959.

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ception because of previous advances in knowledge in the basic biological, physical, and—more recently—social sciences. As medicine has become more and more a precise science, it has become imperative that the clinical investigator himself obtain a sound knowledge of these basic sciences. It is a common experience for a resident, having completed a long and arduous course of training in clinical medicine, to feel inadequately prepared for a career in clinical investigation, however good his medical school basic science education may have been. Hence, he embarks upon further extensive training in a variety of basic sciences, such as chemistry, nuclear physics, or genetics. Yet this resident is usually well past 30 years of age, beyond the period during which many men, in all fields of endeavor, have historically made their greatest contribution. The difficult decisions he must make re-emphasize the need for hard, critical, and continuing examination of the efficiency of all phases of our American educational system.

This need for further basic scientific training is being met in a number of ways. In many clinical research centers biochemists or physicists have joined the clinical groups. Although the presence of such men in daily working proximity does not lessen the necessity for the clinician to understand the major principles of the basic sciences represented, they can provide for him one means by which he can acquire significant basic principles and facts at the same time he is pursuing the clinical problems which challenge him. Were this movement of basic scientists into clinical groups to proceed at a pace which would seriously diminish the number of persons working primarily in their own discipline, it could create an undesirable effect on the basic sciences from which they come. On the other hand, the increasing number of basic scientists participating in clinical fields demonstrates the fortunate recognition that investigation in clinical departments is rapidly becoming inseparable from that carried out in all areas of biological inquiry. A similar intermingling of learning is evident where, either by design or spontaneously, joint or interdisciplinary groups have developed. In these the members, while retaining their own departmental status, are attacking problems utilizing their combined capabilities. The provision of additional individual training in a basic science laboratory may best fit some men's needs, recognizing the adverse influence of prolonging training mentioned above. A possible favorable by-product of return of the clinically trained men to basic science laboratories could be that some of them would elect to remain in the basic discipline. The loss to clinical investigation would be a gain to the basic medical sciences, where recruitment, at least in some areas, is becoming increasingly difficult.

Reference has been made to the place of animal experimentation in clinical investigation. Should clinical investigators, stimulated by observations on patients, undertake to answer questions by means of well-planned experiments in animals? From one point of view, it could be argued that the clinical investigator should limit his activities to the study of sick people and attempt to persuade his colleagues in the basic sciences to carry out the animal experiments. In practice, except for the occasional fortunate blending of interests in a given institution, this is impractical. I would strongly oppose any such limitation for several reasons. First and most important, such a policy is opposed to scientific principle; the true investigator seeks answers to his questions by using any and all means and techniques available to him. Second, society—scientists and laymen alike—has become increasingly concerned with the perplexity of the legal, ethical, and moral aspects of human experimentation since the terrible events of World War II. The proper place of human experimentation poses a difficult and complex problem for which there is no easy answer.[2] In the context of this discussion, I would submit that uneasiness about the extent to which the human should be the experimental subject is undeniably one reason why one finds in most clinical research centers many more rats and dogs than was true a generation ago. Third—but related to both of the above points—many questions originating at the bedside can be more quickly and accurately answered, at least as applied to the animal species used, by carefully planned and controlled animal experiments than by study of the patient. Some experiments on humans are completely impossible; in others they are indecisive; and in many there is anxiety over the degree of hazard to patients or subjects under study. The recent work of Welt, Oliver, Hollander, Williams, Winters, and others, which clarifies the renal structural and functional lesions of potassium depletion as observed in the rat, provide an example of the precision which is possible by utilization of animal experiments to help answer an important clinical question.[3]

Hence, it seems certain that clinical investigation should and will become more closely associated with the rapid developments in all of the basic sciences. This prediction, however, carries with it certain implications as far as clinical research is concerned. The clinical investigator should remind himself periodically that his primary goals are related to the better understanding and treatment of sick people. The approach is less important than the goal. Solution of a problem may involve moving a great distance from the bedside; if, however, the investigator's activities are in an orbit which eventually provides a better understanding of the original clinical question, I would propose that all phases of his endeavor are clinical investigation. Some persons traversing the orbit may find they can make a greater contribution if they stop permanently at some point removed from the clinic or bedside. Until they make that decision, however, it would appear imperative that they keep their clinical skills sharpened by continuing and regular

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association with, and responsibility for, patients on the ward and in the clinic. The speed with which their investigation proceeds may not be as rapid as it would be if they dropped their clinical responsibilities, but the unanswered questions in human illness will inevitably be kept in sharper focus. At the same time, too much patient care and clinical teaching responsibility can and does inhibit the productiveness of many clinical investigators. The provision of adequate time and facilities for the competent investigator is a goal which chairmen of most of the clinical departments in medical schools in the United States continually strive for but rarely reach satisfactorily. Similarly, a chairman's attempts to apportion assignments in order to meet all of the pressing service, educational, and research needs of his particular department are usually only partially successful. Clearly, neither unlimited laboratory space nor funds can insure good clinical research; nonetheless, more of both in liberal quantities will help medicine meet the challenge of keeping up with the growing pace of clinical investigation. The relationship of these needs to medical education and care is self-evident. Unless an atmosphere conducive to continued and productive investigation is provided, the quality of medical education must inevitably degenerate.

In summary, although this is an era in which the potential for the further development of experimental medicine and therapeutics is the greatest in history, the full exploitation of this potential will require solution of many problems, a few of which have been discussed here.

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CHEMICAL EVIDENCE OF INCIDENCE OF HYPOTHYROIDISM

STUDY OF EMPLOYED MEN AND WOMEN, PHYSICIANS, AND PROFESSIONAL BLOOD DONORS

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Determinations of protein-bound iodine levels were carried out on serums obtained from 1,823 men in industry, 2,182 male commercial blood donors, 735 male physicians, and 1,015 women employees of a general hospital. The mean for the first group of men was 5.33 mcg.% with a standard deviation of ±1.19; the mean for the women was 5.67 mcg.% with a standard deviation of ±1.22. On the basis of interviews, physical examinations, and laboratory studies on smaller groups of subjects it was concluded that protein-bound iodine values below 4 mcg.% in men or 4.5 mcg.% in women are diagnostic of hypothyroidism. In these four populations, such evidence of hypothyroidism was found in 4.94%, 9.2%, and 4.2% among the men and 7.3% among the women.

Serum protein-bound iodine (PBI) measurement was used to indicate the incidence of hypothyroidism in 1,823 men employed in industry (fig. 1); in 2,182 male professional blood donors (fig. 2); in 735 physicians who volunteered for the test at the Scientific Assembly of the 107th Annual Meeting of the American Medical Association, San Francisco, June 23-27, 1958 (fig. 3); and in 1,015 women employees of the Los Angeles County General Hospital (fig. 4).

Since the thyroxin circulating in the blood provides 98% of the iodine measured as protein-bound iodine,[1] this chemical procedure determines the level of thyroid hormone which circulates in the blood. The inorganic iodine level was determined and reported in all instances. It is usually below 5 mcg.%. Higher concentrations indicate the ingestion of iodide, which may be bound to the serum protein and produce a "falsely elevated" result. A low result may be due to severe hypoproteinemia, as in nephrosis; to the prolonged administration of

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sodium liothyronine (L-triiodothyronine); or to treatment with large doses of testosterone. It is to be presumed that few of the subjects found to have subnormal levels of protein-bound iodine were in the latter categories. Our accuracy with this method of determination of serum protein-bound iodine level has recently been tested.[2] For

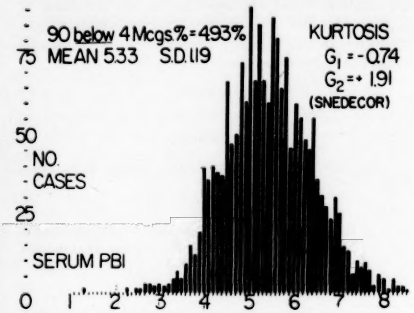

Fig. 1.—Serum protein-bound iodine distribution in 1,823 men in industry; range 1.3 to 8.5 mcg. % inclusive.

example, 11 independent determinations on the same serum from this study had the following values: 4.7, 4.9, 5.0, 4.6, 4.8, 5.0, 5.0, 4.8, 4.8, 4.7, and 4.4 mcg.%, with a standard deviation of ±0.19; 95% confidence limits in normal serum were found to be approximately 0.5 mcg.[2]

Normal Serum Protein-Bound Iodine

The range of normal serum protein-bound iodine level is given by Astwood and associates,[3] Daily and Skahen,[4] Cassidy and VanderLaan,[5] and Peters and Man [6] as from 4 to 8 mcg.%. In their individual series they found that subjects whose level of serum protein-bound iodine was below 4 mcg.% had hypothyroidism. This agrees with the findings in our hospital patient survey which we reported in 1951.[7] We conclude that anyone whose level of serum protein-bound iodine is lower than 4 mcg.% has chemical evidence of hypothyroidism.

Results

The incidence of a serum protein-bound iodine level below 4 mcg.% among the three male groups tested was as follows: 90 (4.93%) of the 1,823 industrial workers (fig. 1); 209 (9.5%) of the commercial blood donors (fig. 2); and 31 (4.2%) of the 735 physicians who had volunteered for the test at the A. M. A. convention held in 1958 (fig. 3).

On the other hand, among the 1,015 female nurses and other female employees of the Los Angeles County General Hospital who had volunteered for the test, only 16 (1.5%) had a serum protein-bound iodine level below 4 mcg.% (fig. 4).

The mean value of serum protein-bound iodine among the male industrial population in our study was 5.33 mcg.%, with a standard deviation of ±1.19 (fig. 1), and in the female employee group 5.67 mcg.%, with a standard deviation of ±1.22 (fig. 4). The calculation of the statistical significance of this difference between these two means results in a possibility of chance of less than one in one thousand (>0.001). Kurtosis calculations [8] were made for each of these populations, and, as expected, it was found that in each of them G_1 was negative and G_2 strongly positive (fig. 1 to 4), thus eliminating the possibility that the distributions might be Gaussian. This indicates that the results are not due to chance and proves that the population is not homogenous.

Clinical Examination

In addition to an interview and physical examination, the laboratory studies done on 64 of the 90 male industrial workers who were available were as follows: repeated serum cholesterol measurement; determination of basal metabolic rate, radioactive iodine uptake, and level of thyroxin-binding globulin; and alpha and beta lipoprotein fractionation by electrophoresis. On the basis of all of these examinations, 3 of these men were considered euthyroid, 21 possibly euthyroid, 20 probably hypothyroid, and 20 definitely hypothyroid.

Assuming that the level of serum protein-bound iodine in the female normally exceeds that of the male by about 0.5 mcg.%, provided the border line between normal and subnormal in the female is placed at 4.5 instead of 4 mcg.%, there were 73 among the 1,015 adult female employees whose level of serum protein-bound iodine was below

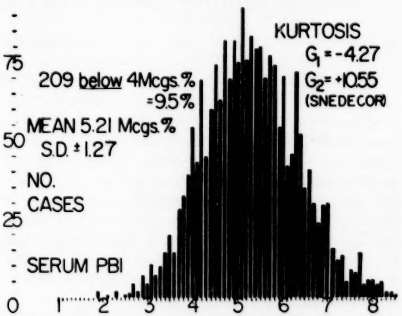

Fig. 2.—Serum protein-bound iodine distribution in 2,182 male commercial blood donors; range 1.9 to 8.9 mcg.% inclusive.

4.5 mcg.%. When 32 of these 73 women were interviewed and reexamined, clinical indications of hypothyroidism were found in 80% of them.

Comment

The present study, with an industrial group three times as large, corroborates our preliminary report,[9] which was based on tests performed on 610 "white collar" workers. In the current study, pro-

vided that only men with a serum protein-bound iodine level below 4 mcg.% are included in the subnormal group, about 5% of the group employed in industry have chemical evidence of hypothyroidism. The fact that, in the United States, more than 20 million men in industry fall into this category indicates the possibility that one million

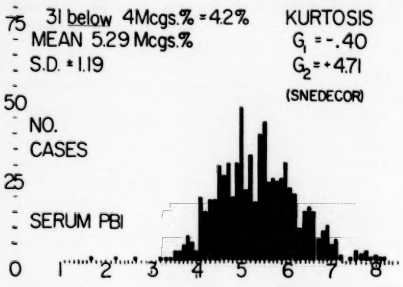

Fig. 3.—Serum protein-bound iodine distribution in 735 male physicians; range 1.7 to 8.4 mcg.% inclusive.

American industrial workers are hypothyroid. Among commercial blood donors the number of men whose level of serum protein-bound iodine is below 4 mcg.% is twice as high as in the industrial group.

The physicians we tested have a slightly lower incidence of hypothyroidism than the men in industry. Considering that there are 200,000 physicians in the United States, and provided that those attending the 107th Annual Meeting of the American Medical Association in 1958 who volunteered for the test constitute a fair sample, these tests suggest that only 8,000 American physicians have thyroid deficiency.

Of most interest is the finding that the mean level of serum protein-bound iodine is definitely higher in a large group of women than in males. This may be the result of the effect of estrogen on the thyroxin-binding globulin, or it may be due to the change in method of determining levels of protein-bound iodine, although there is no evidence of this. Assuming a higher boundary between normal and hypothyroid, 80% of the women having a level of serum protein-bound iodine below 4.5 mcg.% had clinical indications of hypothyroidism. This suggests that the lower limit of normal in adult females be placed at 4.5 instead of 4.0 mcg.% as for males.

Low Level of Serum Protein-Bound Iodine as Indication for Lifelong Substitution Therapy

Given the normal level of serum protein-bound iodine in males as from 4 to 8 mcg.%, a value of 2.66 mcg. is 50% below the mean found in these studies, 3.20 mcg. is —40%, 3.73 mcg. is —30%, 4 mcg. is —25%, and 4.26 mcg. is —20%. On this basis, guided by our long experience with estimations of hypothyroidism based on the basal metabolic rate, it is recommended that men whose level of serum protein-bound iodine is below 4 mcg.% be regarded as having a serious, permanent thyroxin deficiency which requires lifelong provision of thyroid hormone. This should be given in increasing amounts until the protein-bound iodine, which represents the thyroid hormone circulating in the blood, is maintained at a level ranging from 5 to 6 mcg.%.

Summary

Serum protein-bound iodine (PBI) determinations were done on the following groups: 1,823 men in industry, of whom 4.94% had values below 4 mcg.%, the assumed low limit of normal; 2,182 male professional blood donors, among whom 9.2% had values below 4 mcg.%; and 735 male physicians who had volunteered for the test at the 107th Annual Meeting of the American Medical Association, 1958, only 4.2% of whom had levels of serum protein-bound iodine below normal. Of 1,015 female employees of the Los Angeles County Hospital, who had volunteered for the test, only 1.47% had levels below 4 mcg.%. Statistical comparison of the levels of serum protein-bound iodine of the female with those of the male population indicated that the females had a significantly

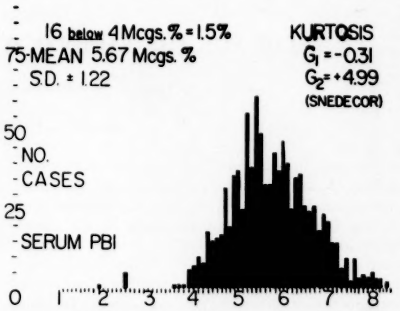

Fig. 4.—Serum protein-bound iodine distribution in 1,015 women employees of a general hospital; range 1.9 to 8.4 mcg.% inclusive.

higher mean level of serum protein-bound iodine, 5.66 mcg.%, with a standard deviation of ±1.22, as against 5.33 mcg.%, with a standard deviation of ±1.19, for the males. It is suggested that a serum protein-bound iodine level of 4.5 mcg.% be accepted as the lower limit of normal in adult females. Subclinical hypothyroidism in American men would appear to exist in about 4 to 5% of the adult male population. Since a serum protein-bound

iodine level of 4 mcg.% is −25% in terms of our mean level of 5.33 mcg.%, it is recommended that men who have values below this be given lifelong thyroid hormone therapy in sufficient daily dosage to maintain their serum protein-bound iodine level at between 5 and 6 mcg.%.

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We wish to extend our thanks to the following persons who were of assistance in providing us with the subjects for our study: the medical directors of General Electric Company, General Petroleum Corporation, Hughes Aircraft Company, Kaiser Steel Corporation, Lockheed Aircraft Corporation, North American Aviation, Inc., Northrop Aircraft, Inc., Richfield Oil Company, Rocketdyne and Atomics International, Southern California Permanente Medical Group, Southern Counties Gas Company, and Union Oil Company; to Dr. John W. Palmer of Hyland Laboratories, Los Angeles, who provided the specimens from professional blood donors; to Dr. Charles E. MacArthur, Chairman of the Section on General Practice, Scientific Assembly of the 107th Annual Meeting of the American Medical Association, San Francisco, June 23-27, 1958; and to Dr. William D. Evans, medical director of Los Angeles County General Hospital, Los Angeles.

We wish to acknowledge the technical assistance provided by Miss Maria Deering and Mrs. Bertha Cook, who made the determinations of serum protein-bound iodine levels for our study.

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V. 1

PROBLEMS FOR THE RADIOLOGIST IN DIAGNOSIS OF GASTRIC ULCER

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and
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Roentgenographic and fluoroscopic examination of the stomach often reveals ulcers whose nature, whether benign or malignant, cannot be determined from appearance alone. The authors believe that when the nature of an ulcer along the greater curvature and prepyloric areas is in doubt, a two-week to three-week trial of medical management is justified. Reexamination after one or two such trial periods should show substantial healing, if the ulcer is benign. If it is not, surgical treatment is indicated. If a patient with gastric ulcer does not secrete hydrochloric acid even when stimulated with histamine, the probability that the ulcer is malignant is much greater, and immediate surgical treatment is recommended.

The radiologist's problems in the diagnosis of gastric ulcers are largely concerned with the detection of small gastric ulcerations, the determination of the benignancy or malignancy of the gastric ulcer, and minimizing radiation exposure to the patient. The latter problem also raises the question of how often reexamination should be done to determine the progress and healing of an ulcer. Modern medical therapy has introduced new factors in the causation of gastric ulcerations which require his attention. Of prime importance is the induction of gastric ulcers in patients on prolonged corticosteroid therapy (fig. 1, *top*). Of less frequent occurence is the development of gastric ulcerations in patients who have had deep x-ray or supervoltage therapy to the upper part of the abdomen.

Read in the Symposium on Gastric Ulcer before the Joint Meeting of the Section on Gastroenterology and Proctology, the Section on Pathology and Physiology, and the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

Gastric ulcers may also be a complication of retained foreign bodies such as phytobezoars and trichobezoars (fig. 1, *bottom*).

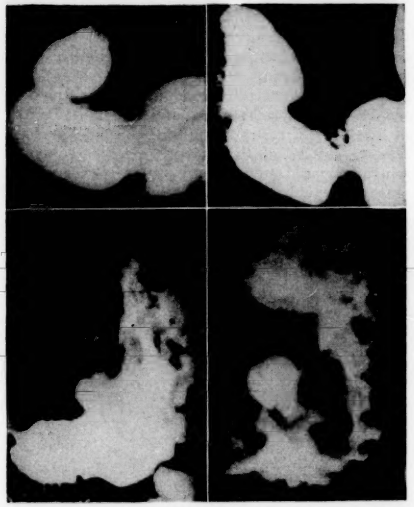

Fig. 1.—*Top* (*left*), acute penetrating prepyloric gastric ulcer induced by prolonged steroid therapy, with (*right*) prompt healing three weeks later. *Bottom*, large penetrating gastric ulcer on lesser curvature resulting from gastric stasis induced by multiple phytobezoars.

that may be either benign or malignant; and (3) the definitely carcinomatous ulcers. The ulcers in group 3 can be quickly disposed of because they are gastric cancers and as such they do not fall within the scope of this discussion.

Method of Roentgenologic Examination

The great majority of gastric ulcers found by roentgenologic examination are benign and fall into group 1. The main problem in patients with this group of gastric ulcers is their early detection and critical evaluation. This requires careful fluoroscopic and roentgenographic examination of the stomach, including a series of "spot films." The examination begins with a study of the gastric mucosa. The patient takes about 2 oz. (60 Gm.) of barium sulfate and is then manipulated in such a manner as to provide a double contrast, with the barium and air used to delineate the pattern of the gastric rugae. This is followed by a detailed study of the gastric mucosa, with use of compression to spread out the gastric rugae and to press barium into any shallow ulcer crater. Fluoroscopic examination of the barium-filled stomach is employed with manual palpation to visualize the entire contour, thus revealing any ulcers to the best advantage both in profile and *en face*.[1] The examination is concluded by filming the stomach in the anteroposterior, lateral, and oblique projections, with the patient in both erect and horizontal positions. Delayed films are valuable in determining gastric emptying and gastric motility. Some gastric ulcers may even be more apparent on the delayed film, as pointed out by MacMoran and co-workers.[2] Only after these measures have been employed can the patient be said to have received a competent and thorough roentgenologic examination. This can be accomplished efficiently, without causing excessive radiation-exposure, by a physician trained in radiology.

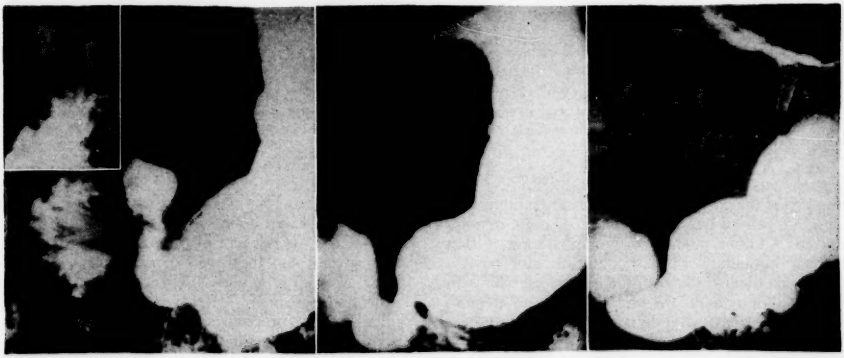

Fig. 2.—Typical acute benign penetrating gastric ulcer in pars media on lesser curvature. *Left*, note demonstration of radiating gastric rugae leading to ulcer crater, indicating a benign gastric ulcer. Roentgenograms made at follow-up examinations, about three, *middle*, and seven, *right*, weeks after institution of medical regimen, showing complete healing of ulcer.

The radiologist's problems can best be organized by dividing all gastric ulcers into three large groups, depending on their roentgenographic appearance: (1) the definitely benign gastric ulcers; (2) the indeterminate group, that is, gastric ulcers

Almost all ulcers in the proximal three-fourths of the stomach can be demonstrated in silhouette, (fig. 2 and 3). Those on the posterior and anterior walls of the antrum and the prepyloric and pyloric areas are best shown by compression technique, since they usually cannot be placed in profile (fig. 4). Fluoroscopic image intensification units have been useful in minimizing radiation exposure from fluoroscopy but have not added materially in the detection of most ulcers. One rule that has proved helpful is to repeat an examination which has given an initially negative result, if the patient's symptoms persist without a satisfactory explanation. Such conditions as patient relaxation, state of hydration, gastric secretion, and fluid retention may change in the interval between examinations, and these alterations may make the ulcer more demonstrable. Another point worth emphasizing is that 15% of patients with gastric ulcers also have a duodenal ulcer.[3] Gastric ulcers associated with gastric hypotonicity are more difficult to demonstrate in patients with hypomotility and retained gastric secretions.[4]

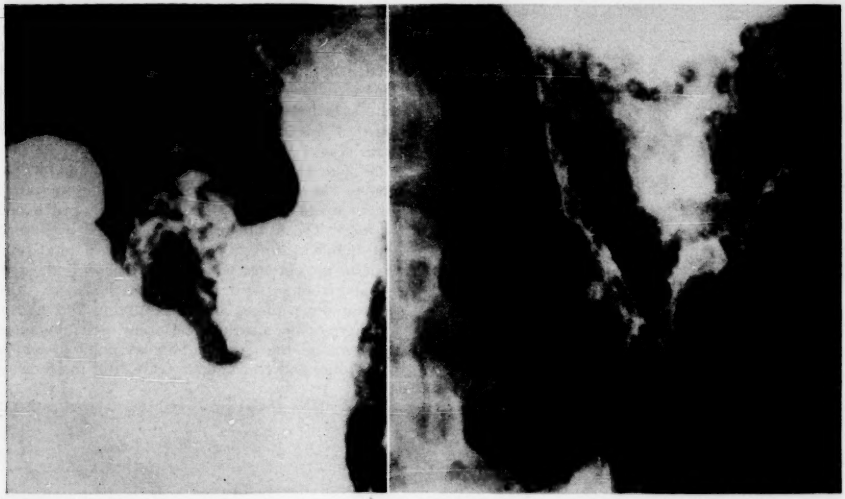

Fig. 3.—*Left*, large penetrating gastric ulcer on lesser curvature, with, *right*, marked decrease in size and evidence of healing within three weeks. Final roentgenologic examination should be made to demonstrate complete healing, to be certain that no malignant change has occurred.

Criteria for and Management of Malignancy

While we believe that we are still finding about five times as many duodenal ulcers as gastric ulcers, we have the impression that gastric ulcers are seen more frequently. Gastric ulcers are still reported as occurring in about the same location and at about the same frequency; about 2% in the cardia and fundus, 65% in the pars media, 15% in the antrum, 10% in the prepyloric area, 2% in the isthmus, and 6% along the greater curvature.[5]

The incidence of simultaneous occurrence of multiple gastric ulcers[6] is increasing from the time-honored figure of about 2% to about 6% (fig. 5). This is probably due to the increased efficiency of the roentgenologic examination in the detection of smaller lesions. Katz and Bierenbaum[6] in a review of cases of multiple gastric ulcers expressed the belief that gastric ulcers are benign when they are multiple and are only occasionally associated with carcinoma.

Reports[7] are accumulating that have altered current thinking about malignancy of gastric ulcers along the greater curvature of the stomach. It now appears that about half of them are benign, whereas not long ago they were considered "malignant until proved otherwise." This same attitude has prevailed for many years with regard to gastric ulcers in the prepyloric area and in the isthmus, yet we are now seeing reports which indicate that this may or may not be so. Elliott and co-workers[7a] in their study of ulcerating lesions of the stomach found that "there is no statistical evidence lending credence to the dogma of 'malignant until proven otherwise' when an ulcer is either large in size or located in the prepyloric area or along the greater curvature of the stomach. Instead it would appear

that there is at least an even statistical chance that these lesions will be benign." These and similar statements by others indicate that location and size of the ulcer are no longer valid criteria in themselves for determining whether an ulcer is malignant.

Do these statements mean that gastric ulcerations have become less malignant? No; we believe that this is due to an improvement in the radiologist's ability to recognize gastric cancer and also to the gastroenterologist's and the internist's abilities to distinguish malignant from benign gastric lesions. Without a doubt, all physicians have developed a better understanding of both of these conditions during the past decade.

week period. Most benign ulcers will have healed in this interval. It is desirable to repeat the roentgenologic examination of the stomach a third time to be certain that complete healing has occurred. If, after application of this therapeutic regimen, reexamination shows that healing is incomplete and there is not complete relief of the patient's symptoms, then surgical treatment is indicated. The therapeutic regimen must be applied much more rigidly to any patients with recurrent ulcers, since the rate of malignancy is much higher in this group.

In actual practice, we have found it difficult to persuade the patients to come back for the third examination and even sometimes for their second examination, because they begin to feel so well that

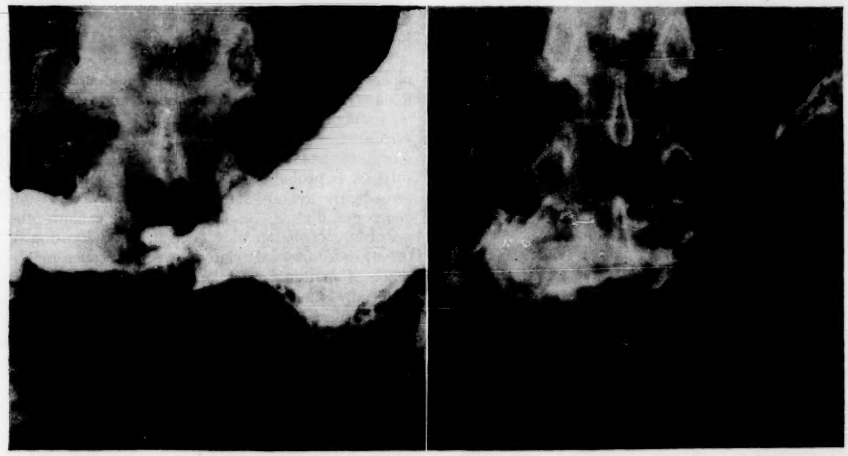

Fig. 4.—*Left*, acute penetrating gastric ulcer in antrum of stomach on posterior wall demonstrated by pressure technique, with, *right*, complete healing in about two and one-half months of treatment by medical regimen.

Assuming these new concepts to be true, are we then justified in advocating the same short trial period of medical management for ulcers along the greater curvature and prepyloric areas as we have for those in the pars media? We think it is justifiable to apply this form of management. The size of the ulcer has little importance in cases selected for medical management. We must, however, take into account the greater cicatricial changes that occur in the prepyloric antrum with healing and realize that about 20% of them will eventuate in pyloric obstruction. We would therefore recommend confirmation of the roentgenologic diagnosis of the benign gastric ulcer and of ulcers in the indeterminate group by applying this trial regimen, with reexamination in two to three weeks. If the lesion is definitely smaller, the medical regimen may be continued for another three-week or four-

they do not see the necessity for the final study. The subsequent examinations do not have to include the entire upper gastrointestinal tract and can be limited to the stomach and performed at a lower cost and with less radiation exposure.

To summarize, the medical regimen test and serial roentgenologic reexamination showing definite evidence of healing constitute the most reliable means of determining that a penetrating gastric lesion is benign. An exception to this rule may be the patient with histamine-fast achlorhydria; these patients are five times as apt to have an associated malignancy and may need immediate surgical treatment. When the possibility of malignancy cannot be dispelled, despite all appropriate laboratory and therapeutic tests, surgical measures become mandatory.

When this practice has been followed, what has been the percentage of error? Elliott and co-workers [7a] reported a 20% excess in overdiagnosing "malignant" or "probable malignant" disease and an error of 6% of malignancies diagnosed as "benign" or "probable benign." This 6% error compares favorably with the accepted roentgenologic margin of error in attempting to distinguish between benign and malignant gastric lesions. Peterson [8] at the University of Minnesota, following a similar practice, has done even better, with a reported 3% error. The 20% overdiagnosed as possibly malignant indicates that "when in doubt" they have been erring on the side of malignancy.

Fig. 5.—Patient with two small gastric ulcers on lesser curvature of pars media and one at pylorus. Multiple gastric ulcers occur more frequently than previously considered. It is also well to keep in mind that 15% of patients with gastric ulcers will also have duodenal ulcers.

The roentgenologic criteria for benignancy in the diagnosis of gastric ulcer depend on several well-established attributes, none of which is pathognomonic. Among them are (1) protrusion of the ulcer crater beyond the stomach wall, with the demonstration of a smooth ulcer floor and contour; (2) demonstration of mucosal folds radiating into the ulcer crater; (3) demonstration of a narrow band of translucency about the neck of the crater formed by a collar of overhanging mucosal edges (Hampton's line) (fig. 3); and (4) absence of induration around the base of the ulcer, with pliable adjacent stomach wall and persistence of peristaltic movement through the area of ulceration. Usually two or more of these characteristics form the basis for the diagnosis, but each lesion is an individual problem and must be evaluated on its own merits and appearance.

Conclusions

In conclusion, from the radiologist's experience the following statements concerning gastric ulcers appear justifiable: 1. More gastric ulcers are being found, a fact due perhaps as much to more efficient roentgenologic examination as to rising incidence. 2. Gastric ulcers are not infrequently multiple in occurrence. 3. The most significant diagnostic roentgenologic finding is the demonstration of an ulcer crater into, or through, the stomach wall. 4. An adequate trial of medical management is almost always indicated, followed by a roentgenologic reexamination to demonstrate complete healing. If this is not feasible, then a surgical approach might be considered at the onset.

5. With regard to the relationship of gastric ulcers to gastric malignancy, the incidence of malignancy in the gastric ulcer which appears benign on roentgenographic examination is extremely low—approximately 3% [8] to 6%.[7a] The incidence of mortality from gastric resection by the average surgeon is probably as high as or higher than the error by the average radiologist. There are no roentgenologic findings which absolutely exclude the possibility of malignancy. The size and location of the ulcer cannot be related to the presence or absence of malignancy. Likewise, these factors have little importance in the selection of cases for medical management. The most reliable and practical method of establishing the diagnosis of a benign gastric ulcer is to institute the therapeutic regimen together with a roentgenologic examination after two weeks, with the demonstration of progressive healing. There is no simple practical clinical test for determining the presence or absence of malignancy in an ulcer.

The radiologist's problems in the diagnosis of gastric ulcers were well summarized by Dr. Leo J. Rigler [9] in 1935 when he wrote, "On the shoulders of the general practitioner lies the responsibility of recognizing the seriousness of gastric symptoms of patients in middle age and of urging early and repeated x-ray examinations.

"Upon his shoulder also rests the responsibility of seeing to it that the roentgenologic examination is done by one who is most competent in the art—otherwise, it may be worse than useless. Upon the shoulders of the radiologist rests the responsibility and also the opportunity of making the diagnosis early and distinguishing it from carcinoma of the stomach so that surgical treatment may have some opportunity for success."

100 N. Euclid Ave. (8) (Dr. Scott).

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CONTRIBUTIONS OF THE PATHOLOGIST TO PRESENT-DAY CONCEPTS OF GASTRIC ULCER

Stanley L. Robbins, M.D., Boston

Gastric ulcers in 243 patients, all of whom were 50 years of age or older, were studied by autopsy procedures, and the data were correlated with some of the presumptive factors in the differential diagnosis of gastric ulcer. The teaching that the benign types of ulcer occur more commonly than those of neoplastic origin was upheld; a 3-to-1 ratio was found to exist and to extend to the 80-year-old group of patients. Classification of ulcers by size and type gave the following information: 10% of the benign ulcers were 4 cm. or more in diameter and 20% of the malignant ulcers were 2 cm. or less in diameter, but in the 53 ulcers larger than 4 cm. the number (33) of neoplasms was greater. No differential diagnostic values could be assigned to the location of the ulcer on the stomach wall. Transformation from a benign to malignant lesion was calculated to take place in less than 1% of peptic ulcers.

While the pathologist has many roles to serve, one of the more important contributions he may make is to reassess periodically his knowledge of the more unsettled issues in medicine. Peptic ulcer, particularly gastric ulcer, is an entity which remains shrouded in many enigmas. Moreover, even our slender fund of knowledge on this subject is riddled by contradictions and confusions. Much that has been said about this subject is controversial, and certain aspects have been overemphasized.

I should like critically to reexamine four points with respect to gastric ulcers: (1) the significance of the age of the patient in the differential diagnosis of benign and malignant gastric ulcer; (2) the significance of the size of the ulceration in the determination of whether it is benign or malignant; (3) the value of the site of the ulcer as a point of differentiation between benign and malignant lesions; and (4) the hazard of the transformation of a benign peptic ulcer into a gastric malignancy.

Materials and Methods of Study

To evaluate these four points, a study was made of 234 cases of gastric ulceration at the Mallory Institute of Pathology of the Boston City Hospital, during the years 1940 to 1949. This included all cases of gastric ulceration, benign and malignant, that occurred consecutively during these years in

Read in the Symposium on Gastric Ulcer before the Joint Meeting of the Section on Gastroenterology and Proctology, the Section on Pathology and Physiology, and the Section on Radiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 10, 1959.

patients 50 years of age or over who came to autopsy in this institution. It therefore represents a largely unselected population that more or less exemplifies the incidence of these lesions in the population of a large municipal hospital. Patients over the age of

TABLE 1.—*Age at Death of 234 Patients with Benign and Malignant Gastric Ulcers*

Age Group, Yr.	Total	Ulcers			
		Benign		Malignant	
		No.	%	No.	%
50-59	48	40	83.3	8	16.7
60-69	80	52	65	28	35
70-79	81	58	71.6	23	28.4
80 and over	25	18	72	7	28

50 years were selected for the reason that it is often said that a gastric ulcer is more ominous in patients in this age group, because older patients are so much more likely to have a malignancy than are younger patients. While these data were taken only from postmortem specimens, it was felt that such a series would, if anything, have a higher incidence of malignant lesions, since benign lesions might have healed and not be represented in this study; and, moreover, since the hospital accepts a great many patients for terminal care, terminal gastric malignancies would have a slightly higher incidence in the final distribution. This higher incidence of malignant gastric ulcer was completely acceptable, however, since it was believed from previous experience that this weighting would only serve to emphasize the points to be made.

It can be seen from table 1 that, even in this advanced age group, with such weighting as may have occurred on the basis of the data already given, in each decade benign gastric ulcers are far more common than malignant ulcers. These data merely emphasize the fact that benign peptic ulceration is more common at all ages than is malignant ulceration of the stomach, and that even in the advanced age groups, 80 years and over, the ratio remains almost three to one, benign to malignant.

The data in table 2 show clearly that, when the benign ulcers are classified according to size, about 10% of all benign lesions are over 4 cm. in size. Conversely, about 20% of malignant ulcers were less than 2 cm. in diameter. The belief, stated many years ago, that a large ulcer is almost always malignant is therefore proved to be incorrect. Considerable emphasis has been placed on the differential importance of the 4-cm. size of the crater. However, it must be appreciated that this differential importance is only relative. It is true that when ulcer craters of 4 cm. and over were analyzed it was seen that there were 20 benign as against 33 malignant lesions in patients in this series. It is therefore perfectly true that in a given patient there is still a more than even chance that a 4-cm. lesion will be malignant, but it must not be forgotten that it may still be benign and, moreover, that the small gastric crater may well represent a malignancy. I should emphasize that even these small malignant ulcers were, in most instances, the primary cause of death of the patient; and all physicians, I am certain, have had the experience of seeing a small ulcerative carcinoma lead to metastases before the primary lesion has caused significant symptoms.

With respect to the site of gastric ulceration, it is evident from the following data that there has also been too much emphasis on the differential value of the location of the lesion. The site of an ulceration has been classified in two ways in table 3.

First, the stomach was divided into the so-called pyloric and prepyloric areas (included together under the heading prepyloric) and then into body and cardia as major subdivisions, and then these same ulcers were reclassified with respect to their location on the curvatures or anterior or posterior walls.

Only those lesions which were well confined to one of these geographic areas were included in this analysis. In this group 58% of all benign lesions occurred in the pyloric-prepyloric region, and 56% of all malignant lesions occurred in the same location. In terms of absolute numbers, the figures indicate that there were 87 benign to 34 malignant prepyloric ulcerations in a consecutive postmortem series. Prepyloric location, therefore, is not indicative of malignancy; in fact, on the pure basis of chance and probability there is at least a two-to-one likelihood that a lesion in this location will be benign. With respect to the classification of ulcerations on the curvatures, it is evident that 14% of all benign lesions occurred on the greater curvature and 39% of all malignant lesions on the lesser curvature. In fact, with respect to location on the greater curvature, the absolute figures reveal 24 benign and 23 malignant ulcers. As one would anticipate, in terms of lesions located on the lesser curvature, the figures are 78 benign and 33

TABLE 2.—*Analysis of the Size of 190 Benign and 68 Malignant Gastric Ulcers*

Diameter, Cm.	Ulcers			
	Benign		Malignant	
	No.	%	No.	%
1 or less	65	34.2	3	4.4
1.1 to 2	62	32.6	11	16.2
2.1 to 3	24	12.6	9	13.2
3.1 to 4	14	7.4	9	13.2
4.1 and over	20	10.5	33	48.5
Unknown	5	2.6	3	4.4

malignant ulcers. Once again the data indicate overemphasis on the seriousness of location on the greater curvature and also indicate that ulcers on the lesser curvature may indeed be malignant, in our present series the proportion is again almost one-third malignant of all lesions on the lesser curvature. However, it must be remembered that

these absolute figures do not necessarily reflect the true incidence nor the true distribution of these lesions in the entire population, since the figures are undoubtedly weighted by the facts that an older age group was dealt with and that the healed benign lesions were not analyzed, and by other factors as well. These data merely indicate that there are no absolute differential values to the location of an ulcer.

The possibility that a benign peptic ulcer may become malignant has, I believe, been overemphasized. The variable opinion expressed in the literature is in large part a reflection of the variable criteria used by the authors of various studies. It is at best difficult to determine whether a gastric carcinoma may have indeed arisen within a pre-existing peptic ulcer. It must be remembered that gastric carcinomas of all varieties may undergo peptic digestion, particularly in a stomach having a highly corrosive acid peptic juice. It is therefore possible for a preexisting gastric carcinoma to assume the appearance of a previously benign peptic ulcer. Such a lesion may therefore be interpreted as malignancy arising in a previously benign process. At the Mallory Institute the criterion has been adopted that if malignant invasion is found in the base of an ulcer as well as in the margins and walls of the ulcer it is more likely true that the lesion represents a preexisting carcinoma arising "de novo." In the rare case in which malignant transformation is believed to have occurred in a benign peptic ulcer, the cancer is generally confined to the mucosal margins of the ulceration, without involvement of the base.

It is true, however, that if the progress of these lesions is followed long enough they will directly invade the entire wall of the stomach and involve the base as well, but at this point it would be impossible to recognize the preexistence of a benign process. It therefore seems unwise to make judgments in patients with far-advanced malignancies, because the landmarks are so obliterated as to make the trail impossible to follow. With the aid of the criteria just set forth it is my contention that malignant transformation occurs in less than 1% of benign peptic ulcers arising in the stomach. I might add a word of caution; the history of a patient's having had an ulcerative process for many years does not indicate that the lesion must have been benign for a long period, because, once again, one encounters undoubted carcinomas that have followed a relatively benign course for years, and there is no precluding the possibility that a patient may have had a benign peptic ulcer that healed only to be followed after some period by a malignancy arising in a totally different site.

TABLE 3.—*Classification of Ulcer Status by Location*

Ulcers	Prepyloric	Body	Cardia	Greater Curve	Lesser Curve	Anterior Wall	Posterior Wall
Benign	87(58%)	52(35%)	11(7%)	24(14%)	78(47%)	21(13%)	44(26%)
Malignant	34(50%)	19(31%)	8(13%)	23(27%)	33(39%)	10(12%)	19(22%)
Total no.	121	71	19	47	111	31	63

Summary

A fresh look at the problem of the differential diagnosis of the gastric ulcerative lesion indicates that even in patients of an advanced age the probabilities are in favor of a lesion being benign on the sheer basis of the frequency of the two kinds of diseases. Size is not of absolute differential value, and location has been grossly overemphasized as an important criterion, as has been the hazard of malignancy developing in a previously benign peptic lesion.

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VIRUSES, INFECTIONS, AND DISEASES.—The older idea of "one disease-one agent" has had to give way to the concept that a well-defined clinical syndrome may be induced by any one of a number of viruses and that one virus may induce several different symptom complexes. The new knowledge has important implications to understanding viral infections of the respiratory tract. As an example, the clinical syndrome called influenza may be induced by some ten or eleven different viruses, only four of which are designated as influenza viruses. Moreover, one influenza virus may induce a wide variety of clinical entities ranging in severity from very minor upper respiratory infections to fatal viral pneumonia. Thus, a diagnosis of influenza may mean quite different things to the clinician and to the virologist. Ideas about viruses, like those about bacteria, are becoming less and less disease-oriented and more and more concerned with the mechanism of infection which may, but more commonly does not, lead to disease.—Frank L. Horsfall Jr., The J. Burns Amberson Lecture, *The American Review*, September, 1959.

SURGICAL MANAGEMENT OF GASTRIC ULCER

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and
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Whether a given gastric ulcer is benign or malignant can be decided only by the pathologist examining the excised specimen. In a series of 155 patients hospitalized with the diagnosis of gastric ulcer, agreement between physician and surgeon that the ulcer was benign occurred in about 7% of the cases. In 5% of the patients the ulceration is believed to have been precipitated by gastric irritants and stimulants, such as medicaments taken habitually. Medical management, including withdrawal of such irritants, should be tried; if this fails a surgical program adapted to the location of the lesion is recommended. The postoperative course of patients with conservative forms of gastric resection was compared with that of patients after radical resections. In a series of 76 patients those with conservative resections were underweight in 42% and troubled with moderate or severe dumping symptoms in 2.6% of the cases, while the corresponding figures for radical resections were 80% and 47%. Routine radical resection for gastric ulcer is not justified by the known incidence of malignancy. Hope lies in better diagnosis and in earlier, rather than more radical, surgery.

The discouraging results in the treatment of gastric carcinoma over the years have suggested the need for more aggressive management of gastric ulceration. So many of the old diagnostic stand-bys have failed just often enough in differentiating a benign from a malignant ulcer to strengthen the surgeon's conviction that early surgery is the logical solution.

While gastroscopy [1] and exfoliative cytological studies [2] have confirmed malignancy in many cases of so-called benign ulcer, most patients in the United States are treated without these added diagnostic facilities. However, regardless of how extensive the studies, the brutal truth remains that every gastric ulcer may be a cancer. Only the pathologist, with the surgically excised ulcer available in his laboratory for microscopic study, can tell for certain whether a particular ulcer is benign or malignant.

It is believed that a more aggressive policy might be developed if a "cancer type" of radical resection were not routinely performed for both benign and malignant lesions. Certainly the patient would benefit. A comparison of our experience, over a five-year period, with routine radical resection for gastric ulcer to that, in a recent three-year period, with more conservative resection has convinced us that the conservative approach is desirable.

Incidence of Unsuspected Malignancy

As in patients with duodenal ulcer, intractable pain, hemorrhage, and obstruction as well as perforation remain the standard indications for surgery. Despite a disagreeably high incidence of recurrence, the physician has relied on medical therapy for uncomplicated ulcers; this is because the odds may be as favorable as 10 to 1 that a well-studied gastric ulcer is benign. He is loath to recommend operation, since he has been more impressed with the disagreeable side-effects of radical resection for what turned out to be a benign lesion than he has been by missing a diagnosis of carcinoma of the stomach.

The physician might favor early surgery more if the surgeon could show overwhelming evidence that early operation for gastric ulcer insures a higher five-year survival rate of patients with gastric malignancy. This is suggested from the experiences of Hayes [3] and Ravdin.[4] In contrast, the surgeon has been pleased with the results of even the most conservative procedures for benign gastric ulcers because of the low incidence of marginal ulceration as compared with duodenal ulcer.

Most patients cooperate medically when threatened with the removal of a large part of their stomach, but they also become increasingly alert to the potential of malignancy. As a result, they resist the idea of prolonged diet and hospitalization.

Continued confidence in the medical treatment of gastric ulcer was apparent from a review of 155 patients hospitalized with this diagnosis during the years 1956 to 1958 inclusive. During this period 42% of the patients with a diagnosis of gastric ulcer were not seen in consultation by the surgeon. Slightly over one-fourth, or 28%, of the patients were subjected to a gastric resection, while in 30% surgery was delayed for a variety of reasons.

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There was general agreement between the physician and the surgeon in approximately 7% of the cases that the ulcer apparently was benign. A longer period of bed rest and intensive therapy was recommended. Although three weeks of hospital treatment has been referred to over the years as the classic trial by medication, it is doubtful if this magic figure is followed generally. As a matter of fact, it is more likely that economics makes it mandatory that many patients remain ambulant and that medical treatment be continued much longer. In 6% of the patients in the present series the immediate surgery was not recommended because of the patient's age or an advanced cardiac condition; these made the dangers of malignancy less than the dangers associated with gastric resection. Another 3% refused surgery. In 5% of the patients gastric irritants and stimulants were believed to have precipitated the ulceration. A program of drug withdrawal and intensive medical therapy was agreed on.

The possibility of a drug-induced ulcer from the ingestion of gastric irritants or stimulants is assuming greater importance in these days of the "coffee break."[5] Furthermore, as the age of the population increases, the incidence of arthritis mounts and relief is sought by self-medication with salicylates and other arthritic "pain-killers." We have been impressed by the number of patients who accept self-medication as so routine that even under close questioning they neglect to mention it. The effect of salicylates, phenylbutazone, and steroids on the upper gastrointestinal tract is well known.[6] On occasion, antihypertensive drugs such as reserpine[7] deserve consideration if the patient's difficulty coincides with the administration of this particular medicament. Finally, excessive use of alcohol would be a strong deterrent to early operation in a given patient.[8] However, the possibility of malignancy is ever present.

It is of the utmost importance to evaluate the probability of malignancy in every patient with gastric ulceration. When malignancy is suspected early operation is mandatory. A strong indication for surgery is the combination of persistent symptoms and roentgenologic evidence of an ulcer despite intensive medical therapy. Relatively few patients would be subjected to gastric resection after a short period of ambulant medical treatment unless they were having so much distress that the relief of pain would be an indication for surgery. When exfoliative cytological studies show suspicious cells in gastric washings, early surgery is mandatory. Patients with these findings should not be included in the statistical study of questionable cases.

The radiologist's opinion about whether the gastric ulceration has the characteristics of malignancy plays a major role in the decision for or against surgery. He should be given the opportunity to restudy the patient if there is any doubt of the diagnosis. If surgery is delayed, the patient's progress must be followed by interval roentgenologic studies. Histamine achlorhydria certainly should be an influencing factor; however, high free acid values do not exclude malignancy. The increasing incidence of gastric cancer in the presence of pernicious anemia is well recognized, and any gastric ulceration occurring in such patients should be resected. The same principle would apply to the patient with a recurrent crater.

If an ulcer is located on the greater curvature or in the body of the stomach the probability of malignancy rises. Of less significance, perhaps, is the location of an ulcer in the prepyloric area. Finally, the value of gastroscopy in influencing the indications for surgery depends more on the ability of the gastroscopist than on any other factor. It must be remembered that the priority of these influencing factors varies with the individual case. Certainly, a combination of several of these provides strong evidence of malignancy.

Many times it is difficult to determine the optimum time for surgery when the evidence favoring malignancy is minimal. In contrast, there is little disagreement about the indication for surgery for emergency complications such as massive hemorrhage, free perforation, or persistent obstruction of the stomach. The complications occurring in gastric and duodenal ulcer are handled in the same manner, but it is advisable to perform biopsies on all gastric perforations.

Conservative Versus Radical Surgery

Like others,[9] we have been impressed with the number of patients with a history of duodenal ulcer. It is important to investigate the type of surgical procedure which may have been carried out previously on the stomach or duodenum. On occasion, previous surgery for duodenal ulcer such as vagotomy with inadequate drainage of the antrum, resulting in a prolongation of the antral phase of secretion, was no doubt responsible for subsequent gastric ulceration.[10]

A survey of surgical experience with gastric ulcer over a six-year period ending in 1955 has been reported by Denkewalter and Watman.[11] During that period a radical gastric resection of 70% or more, to insure removal of the immediate lymphatic drainage area, was routine for any patient operated on for gastric ulcer. They concluded that this approach was too radical, since 80% of the patients had a large part of their stomach unnecessarily sacrificed for a benign lesion. They advised proof of malignancy by biopsy and immediate frozen section before such a radical procedure was performed. During that six-year period 34% of all patients with gastric ulcers admitted to the hospital were operated on. An unsuspected malignancy was found in 9% of these patients.

After these studies we have altered our plan of treatment during the past three years, 1956 to 1958 inclusive. During this three-year period 30% of patients were operated on, with the unsuspected finding of malignancy in 11%. Over both periods of study, which comprised a span of eight years,

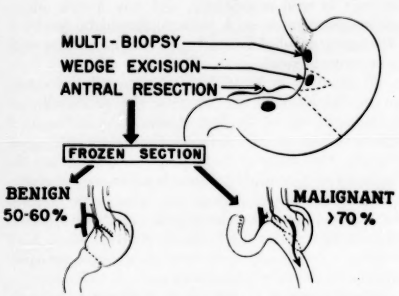

Fig. 1.—Schema of surgical principles employed to avoid radical resection for gastric ulcer. Diagnosis by means of biopsy and immediate frozen section examination allows closure of biopsy site and conservative distal resection, if lesion is benign. Radical resection should be performed only when indicated.

one in every three patients admitted to the hospital with gastric ulcer underwent gastric resection. Unsuspected malignancy was found in approximately 1 in 10.

During the past three years radical gastric resection has been avoided unless there was proof of malignancy by frozen section study at the time of surgery (fig. 1). After a general exploration of the abdominal cavity the location of the gastric ulcer is determined. Any local extension or distant metastasis indicating malignancy is eliminated at this time.

The following program has been adapted according to the location of the ulcer. If the ulcer is located high, near the esophageal gastric junction, evidence of malignancy is sought by opening the stomach and taking several biopsy specimens from around the margin. This is a safer procedure than attempting a complete excision at this high level. If the lesion is proved to be benign by frozen section, the gastrotomy is closed and the distal one-half of the stomach is resected. If the lesion is 5 to 10 cm. from the esophageal gastric junction, the ulcer is excised with a rim of adjacent gastric mucosa. If the ulcer is benign, the wedge opening is closed and a distal hemigastrectomy performed. When the wedge specimen has been taken from the lesser curvature at some distance from the esophagus, the level of resection may be carried out at this point. Occasionally the opening in the lesser curvature is closed and more of the greater curvature is retained for the anastomosis. This is feasible in patients with gastric ulcer since marginal ulceration from excessive hydrochloric acid production is not a problem, as it is in patients with duodenal ulcer. A hemigastrectomy is carried out for an ulcer in the distal one-half of the stomach. If malignancy is found on frozen section study of the resected ulcer, a radical removal of 70% or more is performed, including all of the lesser curvature, 1 in. of duodenum, and the greater omentum.

Certain technical considerations are worth mentioning. In patients with high benign lesions it is advantageous to insure extensive mobilization of the stomach. The greater omentum is detached from the transverse colon as well as the splenic flexure. Further mobilization can be obtained by dividing the vagus nerves and the peritoneal attachment of the fundus of the stomach. The spleen is extensively mobilized by careful and complete incision of the splenorenal ligament. As a result, the fundus of the stomach as well as the spleen can easily be mobilized into the wound and held into position by the placement of a folded towel above the spleen. The left gastric artery and vein are often ligated to facilitate the excision of high-lying ulcers. In such high lesions the removal of the xyphoid process or splitting of the sternum, as recommended by Wangensteen,[12] is helpful.

In performing the wedge excision or biopsy, soft intestinal clamps are applied above and below the ulcer as well as across the left gastric artery and vein. This is done in an attempt to avoid contamination, provide hemostasis, and lessen the chance of distant spread of tumor cells, should the lesion prove malignant.

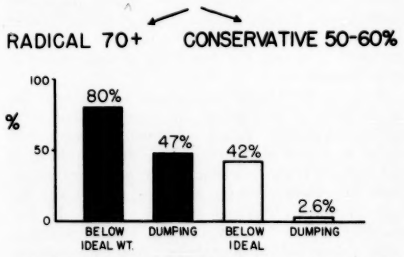

Fig. 2.—Comparison of effects of two types of resection on nutrition and "dumping" symptoms in 76 patients, 38 of whom underwent each type.

If the pathologist finds the ulcer is malignant, it is necessary to remove the lymphatic drainage area of the entire lesser curvature and ligate the left gastric artery at its base. The entire omentum is resected along with 1 in. of the duodenum, depending on the location of the neoplasm. The type of anastomosis constructed depends on the desires of the surgeon. We tend to use the Billroth 1 type; this, in our

opinion, is usually technically feasible and will insure a better chance for good postoperative nutrition with fewer postgastrectomy complaints.

Comment

The study of a limited number of cases has supported the use of the more conservative approach to the treatment of a patient with gastric ulcer proved to be benign by frozen section examination (fig. 2). In a series of 76 patients whose progress was followed for more than one year (half of whom had a radical resection and the other half a conservative resection) the difference is apparent. Of those having a radical resection before 1955, 80% were below their ideal weight; about 47%, or almost half, had dumping symptoms of a moderate degree, although only a few were particularly severe and troublesome. In contrast, only 42% of patients treated during the past three years, most of whom have had a more conservative type of resection, were below ideal weight, and the incidence of moderate to severe dumping was relatively insignificant (2.6%).

Perhaps the surgeon has been so gratified with a low operative mortality and disappearance of ulcer symptoms after radical resection for benign lesions that he has overlooked the high incidence of undesirable side-effects. With less radical surgery the mortality is even lower and the chance of recurrent ulcer symptoms is unchanged. While the incidence of recurrent ulceration is relatively low, it has seemed to us that radical gastric resection has had as much adverse effect on a patient with a benign gastric ulcer as a similar procedure has on the patient with duodenal ulcer. In part this may be due to the fact that the percentage of women subjected to gastric resection for gastric ulcer is much higher than that for duodenal ulcer. It is fairly well established that the end-results in gastric surgery for women leave much more to be desired than do those in men.

Although the number of cases is relatively small, we are convinced that investigation of a larger series of patients treated by this conservative approach after the establishment of accurate frozen section diagnosis is warranted. Perhaps, with the improvement in the total end-result of such surgery, more patients with gastric ulcer will be readily recommended for surgical extirpation of their lesion and thereby the opportunity for early removal of small malignancies will be enhanced.

Summary

Because of the relatively high incidence of unsuspected malignancy, surgical consultation is desirable for every patient with gastric ulcer. This physician-surgeon cooperation is just as important as their dual responsibility in the management of massive gastric hemorrhage. More consideration should be given to the role of drugs, gastric irritants, and stimulants in the etiology of gastric ulcer. Perhaps surgery should be delayed until such drugs have been withdrawn and a trial of intensive medical therapy has been carried out.

Routine radical resection for gastric ulcer is not justified just because malignancy occurs in one case out of 10. This is especially true for lesions high on the lesser curvature, where almost total gastrectomy may be carried out for a benign lesion. Several biopsies or wedge excision of the entire ulcer, with frozen section, should precede radical resection. There should be wider application of closure of the gastrotomy wound for high-lying ulcers, and more distal conservative 50% resections should be performed.

From a nutritional point of view, radical resection for gastric ulcer probably does not insure any better results than does resection for duodenal ulcer. However, the incidence of recurrence of marginal ulceration is much lower in patients with gastric ulcer. Better nutrition and fewer disagreeable side-effects will result with frozen section diagnosis and conservative resection. It is hoped that earlier surgery for more patients with unsuspected malignancy will result in improved management of gastric cancer.

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NEWER CONCEPTS OF SCHOOL HEALTH SERVICES

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For the effective care of a school child with either physical or mental handicaps a complete diagnostic picture is essential. It cannot be provided by the parent or the physician or the teacher separately, for each sees different aspects of the child's problem. Various ways of bringing together the necessary information are here described. A school medical adviser can review the available data with the school psychologist and then discuss the findings with the private physician. In communities where there are medical schools, diagnostic evaluation centers can be set up and their findings interpreted to the family by the general practitioner or the pediatrician. In any case, the diversity of health, behavior, and learning problems is such that the school health program must be viewed as a teamwork project with emphasis on the role of private medical practice.

The concepts of school health services treated here have arisen from developments in medicine, public health, and education in a growing suburban county not unlike suburbia elsewhere. We place new emphasis on private medical practice. This has been possible because of progress in health department staff education, which has stressed diagnosis and treatment as essentially the functions of private physicians and not of health departments or schools. This concept is by no means new, but the increase of medical attention received by school-aged children in our community today has prompted us to recognize a new role for the private physician in school health services.

The development of our policies has been shared with our medical society and the school administrative staff so that private practice has been encouraged as a fundamental policy. This has involved the "concept of the school health program as a teamwork project," [1] which has been demonstrated in an unsurpassed manner by the National Conference on Physicians and Schools, sponsored by the American Medical Association. The teamwork of these national conferences has set a pattern for achieving agreements "despite widely differing backgrounds" of the participants. This has been a challenge for our local application involving several hundred practicing physicians, several thousand school personnel, and nearly 100 health department staff members.

While this paper treats of general concepts, the discussion is largely concerned with handicapped children, because our situation calls for it. The challenge of applying the teamwork approach in Montgomery County has led us to realize the importance of the coordinating function of the health department in its relation to private practice but also to other community resources. Such coordination in our opinion has performed a function that is appropriately governmental only when it cannot be done by people for themselves or by their private physicians.

We show how the need for this coordinating function is most urgent in connection with the medical problems of handicapped children who have had or may have private medical attention. We have found that this function also improves the relationship between the health department and the medical society.

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We are pleased to note that our policies are consistent with those stated in "School Health Services," [2] a report published in 1953 and at that time the last word as a "guide for health procedures in small or large school systems." We shall discuss the school medical adviser as an essential means for carrying out the coordinating function with a new emphasis over the report of 1953.

Recent Changes

Medicine.—The benefits from our newer knowledge in medicine have probably had no greater impact anywhere than on the children in these newer communities. Pediatricians and general practitioners both have been in great demand for advice and health supervision. Preventive medicine has never been more effective, and so the advice of the private practitioner has been in demand not only for illness and prevention but also for the child with developmental anomalies, learning difficulties, and emotional disturbances.[3]

Public Health Practice.—Public health practice in new communities has been generally effective in communicable disease control. Individual housing, sanitation, and environmental problems are minimal compared with other problems. As health depart-

ments, medical societies, and the voluntary health agencies with specialty interests have discovered how much they have in common, public health practice is becoming more and more concerned with problems of mental health, chronic disease, rehabilitation, and diagnosis. This is the field of public health practice which requires community organization and action today. In that sense it is like the social action that was necessary to prevent epidemic disease such as typhoid and diphtheria at the turn of the century.

The neglect of diagnosis, treatment, and rehabilitation for chronic disease, mental illness, and mental deficiency is today as surely the business of public health as neglect of epidemic disease was 40 years ago. We must be concerned not only for humanitarian reasons but also because this burden falls on all of us.[4] We know full well that there is a breaking point beyond which the stress and strain of chronic disease, mental illness, mental deficiency, disability, crippling handicaps, misery, and hopelessness cannot be endured. We are challenged by this broad social problem and the role that medicine, public health, and education can play through teamwork.

Medicine and public health practice have made a splendid beginning for the relief and prevention of these conditions in children. There are many encouraging signs for prevention on all fronts. Some conditions can be cured; many can be compensated; most of them can be alleviated. When the trusted family physician, auxiliary medical services, and public health and school personnel can pull together, family and loved ones can always be comforted. This teamwork improves the prospect of all benefits. It is this pulling together on health problems which is particularly the role of public health practice. Only through cooperation and unified policy can medical practice and education make the proper use of all the medical and social resources which are essential for the relief and prevention of these causes of misery and inadequacy.

Education.—Recent changes in education have not been limited to keeping up with the growth of the school population. The schools are indeed catching up with the concept of the White House Conference of 1930, which emphasized the rights of crippled children to an equality of opportunity. Schools are recognizing the true economy of education and physical care for the handicapped to produce self-supporting and useful citizens and are beginning to alleviate the burden on society of handicapped children who will always need a protecting environment.

Many forces are contributing to this enlightened interest in the handicapped and otherwise exceptional child. Not the least of these forces have been the courageous parents of cerebral palsied and mentally retarded children. They have dared to face the world as parents of children with limited gifts, and they have organized to challenge our apathy and shortsightedness in excluding these atypical ones from public schools. Social and psychological researches have contributed new concepts concerning individual differences so that we no longer look on slow learning, mental deficiency, and various handicapping conditions in terms of heredity. There is even some evidence of the growth of the idea that individual persons have the right to develop their inborn potentialities.

For many years the idea of education for all the children has gradually been contributing to a broader interest in the education of handicapped children. This has led to many demonstrations of special education methods. Carefully selected and dedicated teachers have helped to build up evidence indicating that many types of exceptional children can benefit from special education. Children who are restless, overactive, and highly distractible usually interfere with the learning of other children; yet the skilled teacher with a small enough class can provide a structured situation so that learning can take place.[5] To be managed effectively aggressive children who are emotionally disturbed may also require special teaching skills and small groups.

Whenever the child who interferes with the learning of other children has been removed from a regular class, the improved opportunity for normal children has been so obvious that those who see the improved learning immediately recognize the value of special education. Principals and teachers thus recognize how special education benefits both the children in regular classes and the children who are handicapped. This idea has spread so that it is beginning to play a part in the remarkable advance in special education.

New Demands and New Opportunities

The major public health problems of school-aged children in new suburban communities are no longer the control of communicable diseases and the finding and correcting of physical defects.[6] We still have these problems with us, but they no longer require a major portion of the time of public health nurses and school physicians. Where many children have health supervision through private medical practice, only occasionally is it necessary for public health nurses and school physicians to do things to and for children. We now have an opportunity to tackle, through school health services, some of the problems that may lead otherwise to the breakdown of families, nonproductive citizens, dependency, delinquency, and the problems of children who are already a drag on the regular classes in school.

Both private practitioners and educators are facing more and more demands for advice concerning handicapped and emotionally disturbed children. As educators place more children in special classes,

they gain a clearer focus on atypical children, revealing many with symptoms strongly suggestive of the need for special studies and medical advice. The high cost of special education gives the educator particular concern for the placement of the right children in appropriate special classes. Almost invariably special education supervisors and teachers recognize atypical children who need careful diagnostic studies.

From the educator's standpoint, the answer to this problem of diagnostic studies is usually a referral of all children to a polyclinic or diagnostic center whenever the parents cannot produce an impressive medical report. Educators are usually not aware of the fact that a pediatrician is the coordinator of the medical specialties for children in any diagnostic center nor of the extent of the medical study which may have already been given by the private physician. On the other hand the physician may not be aware of symptoms and behavior observed by the teacher which influence the child's ability to receive an education and the school's ability to educate him. School health services can bring closer understanding to the interpretation of medical and educational viewpoints for the child in question. This important concept will be amplified in the following paragraphs.

From the public health administrator's standpoint the problem is not so much to provide services for handicapped and disturbed children as to see that the community has a mechanism by which physicians and parents are able to use effectively the medical resources of the community. This function of coordination of activities and resources was described in an official statement of the American Public Health Association adopted Nov. 1, 1950.[7] We would add that it is a responsibility of both the public health administrator and organized medicine to take the lead in the development of medical resources when qualified medical, auxiliary, and hospital facilities already established cannot meet children's needs.

Today's Problems

We have pointed out how changes in medical practice have come from advances in preventive medicine, regular child-health supervision, and an ever-increasing proportion of the school-child population being served by a closer doctor-parent-child relationship. From both parents and physicians in recent years we have noted that more parents discuss their child's school problems with their private physicians, and our impression is that this is the result of the gain in child care that has come from more health supervision and closer doctor-parent-child relationships.

As private physicians have called on us to find out how their young patients were getting along in school, we have recognized how difficult it is for the private physician to learn what the school staff have observed about their patients and what they can do for them.

Ordinarily, in office practice the private physician can learn what goes on in school only from the parent and the child. For the child above primary age the skilled physician may, of course, learn much of what is disturbing the child by an indirect approach to the youngster. But parents find it difficult to be objective about their own child. Rarely are they able to evaluate the teacher's competence. The standardized group test results are not well understood by the parent. Even when the school has considerable objective data from the school psychologist, the parent cannot give a reliable report.

The chances are that school personnel do not appreciate the medical aspects of children's problems. Neither do they understand the potentialities of the doctor-parent-child relationship and how much it may contribute to a wise decision for a definitive consultation or effective treatment. They may even recommend with all the authority of the school system that a parent seek a particular kind of specialist. Just as frequently they assume that they can deal with a problem because they believe they can recognize a situation calling for medical help. School personnel often do not know when a child is under treatment or whether the private physician has the background information that is essential to understand the child's behavior.

As we have seen how confused some parents and teachers have become when they encounter different advice from physicians and educators, we have come to the conclusion that coordination between medicine and education is a major problem. Most children with emotional and learning problems are not studied by child psychiatrists. We are not convinced that it is necessary. At any rate, at this stage of our knowledge, physicians and educators need to be aware of problems such as Dr. Lauretta Bender * mentions in her studies, e. g., "an educational problem in children variously designated as learning disability (including reading, spelling, and writing disability), language retardation, developmental or maturational alexia, dyslexia, dyslalia, or aphasia, word deafness and word blindness, or cortical deafness and blindness." When these conditions are a part of the picture, it is particularly important that educators and physicians give advice with some agreement.

School Medical Adviser

For children with multiple handicaps and particularly anxious and confused parents, we have noted how often educators and private physicians try to coordinate their advice to parents. However, they usually fail to get together because it is just too difficult. To deal with this lack of communication we have employed pediatricians on a session basis to go to schools by appointment and consult

with the interested school personnel. Such school medical advisers can understand the viewpoints of both educators and private physicians. They can benefit from the observations of the child in school and can interpret the school situation to the private physician. Reports from the school psychologist are particularly valuable when the school medical adviser can review the data first hand with the psychologist and then discuss the findings with the private physician.

The role of the school medical adviser is equally important to the school personnel when the insight and knowledge of the private physician is brought back to the school and interpreted by the pediatrician. With this liaison we can also insure the proper use of medical resources for diagnosis, treatment, and counseling of parents.

The challenging character of the complex problems of handicapped children is sufficiently interesting for well-qualified pediatricians to be interested in this service. The interchange of information with school and medical observers provides experience contributing to an understanding of the mental health of children. With good nurse-teacher rapport the nurse has an opportunity to learn which children have learning and behavioral problems. If she is well qualified with knowledge of growth and development and child psychology, she can interpret to school personnel the value of the medical point of view. On the other hand, public health nurses may need the encouragement and support of competent supervision in order that the school principal and the personnel worker among the pupils may recognize these values. In our experience it is not enough merely to offer a channel of communication between education and medicine. It must be demonstrated.

One of the best opportunities for demonstrating the value of communicating with the private physician and the contribution of the pediatric adviser is when the child is being considered for placement in the special class. Up to this point it is difficult for school personnel to appreciate the role played by the private physician in planning with the parent for diagnostic studies, therapy, or counseling. Until demonstrated there is little awareness of the parents' confidence in the private physician or the significance of the doctor-patient relationship gained through services in sickness and in health.

The value of a doctor-to-doctor telephone discussion of the child's problems is well demonstrated when the private physician has already been working on the problem. For example, the important role of the private physician is obvious when school personnel learn that the child's behavior can be understood in terms of significant social and family history known to the private physician, that the child is under treatment for a convulsive disorder, that psychological studies have already been recommended by the private physician, or that psychiatric help has been prescribed. When school personnel think a particular kind of medical specialist is needed to help them understand the child, the pediatric adviser in the school can make clear the value of communicating with the private physician by interpreting the special studies already made, by explaining the diagnostic steps that are indicated, and by arranging for such diagnostic service with the private physician.

Such demonstrations for prospective special-class children can bring about a realistic integrative approach to the dynamics of growth so that school, parents, and private physician can work together in the interests of the child. Demonstrations for special-class children open the door to the school medical adviser to be invited to the school for children with less severe handicaps.

We have noticed there is a great deal of discussion in both educational and pediatric circles about the interdisciplinary approach to problems of learning and behavior of children. While there is awareness of the problem, we have not been able to see how it can be met without a pediatric adviser as liaison. The turnover of professional staff in the schools and among public health nurses is sufficient to require continued staff education and demonstrations to achieve teamwork involving both medical and educational judgment. In fact, the professions of medicine and of education both have strong traditions for cooperation within their own groups, but they unconsciously tend to extend their own qualifications—from medicine to education and from education to medicine. As James Harvey Robinson said, "Men are ordinarily peaceful within their group, or at least do not exhibit their individual pugnacity in any deadly form; but let the ancient, inherited group spirit be aroused, and the most highly cultivated men will rush to arms. . . ."

Diagnostic Evaluation Centers

Most communities that have faced up to the high prevalence of physical, mental, and emotional handicaps have set up diagnostic facilities to avoid neglect of children when cost may interfere with the diagnostic studies. For those communities with a medical school, the diagnostic evaluation center generally provides facilities for professional medical training as well as services for handicapped children.[9] However, a diagnostic evaluation center or a group of clinics in a hospital is not the only way to achieve cooperation among medical specialists. The general practitioner or the pediatrician, who knows the family and who is the trusted medical adviser, can coordinate and interpret the findings of the specialists.

Whether there is a well-organized university medical center with an interdisciplinary diagnostic clinic set-up or whether all the studies are done by private specialists, on referral, with the coordination by the private pediatrician or family physician,

there is still need for coordination of medical judgment with the educator's judgment if we are to consider all the disciplines that are involved in understanding the child. For the more complex problem of those with multiple handicaps, men of both medicine and education should have an opportunity to give their interpretation of the child's abilities, disabilities, and functional development as well as his dysfunctions. The concomitant handicaps which result from his primary handicaps should be interpreted from both the medical and the educational standpoints. Thus, a motor defect may interfere with the development of his mental potentialities, or a speech difficulty may delay his social adjustment.

We have emphasized the difficulties of medicine and education, both of which attempt to consider separately the same facts about a single child. We cannot bridge this gap between the two professions without joint planning to achieve an acceptance of the principle that both professions are needed to place the right children in appropriate special classes. In our experience the school medical adviser can bridge this gap.

Summary

In the application of the "concept of the school health program as a teamwork project" in a new suburban county of generally high economic status, emphasis has been placed on the role of private medical practice. Changes in medicine, public health practice, and education relating to school health services and the coordinating function of the health department have called for more attention to children with such handicaps as learning disabilities, mental deficiency, emotional disturbances, epilepsy, defects of speech and hearing, cerebral palsy, and other crippling conditions. Experience with these problems has indicated the limitations of educational planning for such children when there is no satisfactory liaison with the medical profession. The work of part-time pediatricians as medical advisors can bridge the gap between medicine and education.

Box 471 (Dr. Peeples).

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HYPNOSIS IN PAINFUL TERMINAL ILLNESS.—Hypnosis is a state of intensified attention and receptiveness and an increased responsiveness to an idea or to a set of ideas. There is nothing magical or mystical about it. . . . Normal everyday capacity for intensely directed attention can be employed to concentrate and redirect a patient's attentiveness and responsiveness in an altered fashion so that he benefits through a new and learned responsiveness to selected stimuli. This constitutes the use of hypnosis in painful terminal disease. . . . Three case reports indicate definitely that hypnosis can be of value in treating terminal painful illness. However, it is not to be regarded as an absolute answer to all the medical problems involved. Rather, it is one of the possible approaches in the handling of the patient's problems that possesses special and highly significant values at both psychological and physiological levels. While hypnosis can sometimes be used alone as a means of pain control in carcinomatous disease, more often it is properly used as an adjuvant. In that capacity it can serve to diminish significantly the actual drug dosage and to effect a much greater relief both mentally and physically. In all probability, the more comprehensive psychologically the hypnotic approach, the greater is the possibility of therapeutic results.—M. H. Erickson, M.D., Hypnosis in Painful Terminal Illness, *The Journal of the Arkansas Medical Society*, July, 1959.

HORIZONS IN PATHOLOGY

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The history of the Section on Pathology and Physiology reveals changes of name and shifts of emphasis that reflect the developments in both sciences since 1859. The recognition of pathology as a specialty followed the development of microscopy, and the formal training of specialists in pathology began in 1886. The rapid developments of the past 50 years justify certain predictions as to the future. Laboratory tests, largely mechanized to increase accuracy and facilitate handling of results, will be adapted to extensive screening programs. Pathology, while maintaining its status as a basic science, will emphasize its application to patients in hospitals, and medical students will be more regularly assigned to clerkships in clinical pathology before beginning their regular ward service.

We celebrate this year the 100th anniversary of the Section on Pathology and Physiology of the Scientific Assembly of the American Medical Association. Six other Sections are also observing their centennials in 1959.

The line of descent of our Section begins with the Section on Anatomy and Physiology, which was one of the four sections originally proposed in 1859.[1] A continuity of sorts has been maintained by joining the word Physiology to the title of first one and then another section of the Assembly. In sequence the title changes of the Section were as follows[1]: Medical Jurisprudence, Physiology and Hygiene (1865); Practical Medicine, Materia Medica and Physiology (1873); Practical Medicine and Physiology (1890); and Physiology and Dietetics (1891). This section was subsequently joined with the Section on Pathology and Bacteriology, which had been organized in 1900, to form the Section on Pathology and Physiology (1901).

For its first few years the Section on Pathology and Physiology was intimately related to the scientific exhibits of the Annual Meeting. Both the organization of the Section and development of exhibits were proposed by Dr. W. W. Keen, the noted Philadelphia surgeon, in his presidential address before the Association in 1900.[2] Dr. Keen appointed two committees, one for each purpose, with Dr. Frank B. Wynn of Indianapolis as secretary of both committees. Dr. Wynn was undoubtedly chosen for this double honor because he had been successful in forming an exhibit for the annual meetings of the Indiana State Medical Society. In 1897 this exhibit consisted of pathological specimens contributed by the members of the state society.[3] Repeating his appeal in subsequent years, Dr. Wynn had accumulated some 800 specimens by 1899. The Indiana Society was so enthusiastic in its endorsement of this teaching display that it appropriated $300 to ship the exhibit to Columbus, Ohio, where the Annual Meeting of the American Medical Association was held in 1899, one month after the exhibit had been shown at the state meeting. This was the only purely scientific exhibit at the meeting in Columbus, and as such it attracted a great deal of enthusiastic attention.

This pathological exhibit was the beginning of the Scientific Exhibit, which is such an outstanding feature of the Annual Meetings of the American Medical Association. Dr. Wynn served as Director of the Scientific Exhibit until 1916 and expanded its scope to include all of medicine rather than pathology alone.[4]

I have traced briefly the history of our Section since its founding 100 years ago. Now I shall review the development of the science of pathology in America, to provide perspective for a look into the future.

Development of Pathology in America

One hundred years ago "pathology" was the hobby of many American physicians and surgeons who collected and preserved specimens as tangible evidence of their enthusiasm for science. In particular the teachers of medicine in these early times prided themselves on their specimens and used them to make their lectures more vivid and understandable. These specimens were the visual aids for teaching medicine in that era. Thus we have the formation and growth of pathological museums in American medical schools, patterned after those in Germany and England.

Note that so far I have referred to pathology and have not spoken of the pathologist. This is because in those early years pathology both here and abroad was "the practical concern of all progressively minded physicians and surgeons" rather than the domain of a specialist.[5] It was a side line, not a field of practice. In our medical schools the chairs of pathology were usually occupied by practicing

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Chairman's address, read before the Section on Pathology and Physiology at the 108th Annual Meeting of the American Medical Association, Atlantic City, June 11, 1959.

physicians or surgeons, and it was not at all uncommon to recognize the accomplishments of the professor of pathology by rewarding him with the chair in medicine or surgery!

The appearance of the pathologist as a specialist can be traced to the development of the microscope as a tool for medical research and clinical investigation. The microscope opened up entirely new vistas in organ structure and function, in microbiology, neoplasia, and other fields. But before one could explore these promising frontiers it was necessary that he become proficient in the technical skills required for the use of the microscope itself. The preparation of thin transparent sections for staining and examination required a knowledge of the practical chemistry of fixatives, dehydrating agents, solvents, mordants, and dyes. Even after these skills had been learned, one had to acquire sufficient experience to make valid observations, to distinguish fact from artifact. All of this required time and special training and made pathology a vocation instead of a hobby. The pathologist appeared as a specialist, and the microscope marked his crest.

Prior to 1886 there was no opportunity for the training of specialists in pathology in the United States. There was no one here competent to teach the subject, and there were no facilities for instruction in the field. In 1886, after several years' study in Europe under some of the most noted teachers of his time, Dr. William H. Welch, at the Johns Hopkins Hospital and Medical School, offered the first course in America for the practical instruction of physicians in pathology and bacteriology.[6] From Dr. Welch's laboratory at Johns Hopkins came the first American trained pathologists, and from them in turn has sprung the specialty of pathology as we know it in the United States today.

Clinical Traditions of American Pathology

Welch emphasized the importance of a close relationship between the pathologist and the clinician and insisted that the department of pathology be located in the closest possible proximity to the hospital wards.[7] Nevertheless, pathology developed for a number of years along the lines of the other basic sciences in the medical schools rather than as a clinical science in the hospital. Undoubtedly this orientation toward research was necessary before the new science could have clinical application.

Today it is generally recognized that pathology is both a basic science and an important clinical specialty for service to the patient. As a clinical specialist, the pathologist provides definitive answers to specific questions regarding a patient's illness. Does this patient have diabetes? Will this patient's anemia respond to iron therapy? Is this patient's breast lump cancer? When the pathologist provides the answers to questions such as these in the care of individual patients, he is functioning as a clinical consultant. This is the sense in which the terms clinical pathology and clinical pathologist are best used, as pointed out by McMenemey.[5]

Pathology must always be oriented toward clinical medicine and the hospital. Proficiency in pathology can no more be achieved in the isolation of the medical school or research institute than can surgical judgment be acquired in the experimental surgical laboratory. We need constant reference to the day-to-day routine of the hospital to give breadth and depth to our teaching, research, and practice; without this source of new ideas and this testing place for old ideas the dimensions of our specialty tend to become shallow and narrow.

Ever-Widening Scope of Clinical Pathology

The field of pathology has grown rapidly in the last 50 years as a result of the clinical application of fundamental research. We should always remember the debt our specialty owes to the research workers in the other basic sciences. As Davidsohn * has noted, it is in clinical pathology that "yesterday's research becomes today's routine."

It is my opinion that the scope of clinical pathology will continue to expand indefinitely. Whereas some specialties, notably syphilology, have experienced a shrinkage of their fields as a result of the contributions of research, the opposite is our prospect. From my own experience I would estimate that the number of laboratory tests performed in relation to a given number of hospital beds has increased by about 50% in each of the last two 10-year periods. Part of this increase is due to the shorter patient stay and the resultant greater proportion of acutely ill patients within a given bed capacity. Even more, however, is the increase due to the fact that the up-to-date clinical pathology laboratory has more to offer, both in the variety of tests and in their dependability, than did its counterpart 10 years previously.

This rapid expansion of services accounts for most of the pressing problems which confront the clinical pathologist today. First and foremost, we find that no one pathologist can possibly encompass all that must be known for the proper expansion and development of laboratory services. A hospital that required only one pathologist 10 years ago now needs two. The answer, I think, is in the group practice of clinical pathology, each member of the group bringing certain special qualifications and interests to supplement those of the other members of the group.

Second, there is a perpetual shortage of those skilled laboratory workers who are so necessary for the expansion and diversification of our services. Certainly we must look in a number of different directions for the answer to this problem. We must recruit and train increasing numbers of highly skilled, professional medical technologists, and we must see to it that they are well compensated. They

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must work at the highest level of which they are capable, leaving the less skilled tasks for those less qualified. In order to avoid an increase in costs, we must increase the productiveness of our staff by making full use of automatic and mechanical equipment.

Third, there is the widespread problem of crowding in the laboratory. Probably no other division of the hospital outgrows its space allotment as quickly as the department of pathology. The increased number and variety of tests necessitate a larger staff and more equipment; extra bench and office space are needed to accommodate them. In new hospitals space should be provided over and above estimated immediate needs so that pathology laboratories will not already be inadequate before the assigned space is occupied, as is often the case now.

Anticipated Changes in Clinical Pathology

I predict that the next 10 years will see a tremendous increase in the use of laboratory tests for the screening of presumably healthy persons. Such tests, used thoughtfully to supplement the standard physical examination, can be very effective in revealing potential sources of trouble in well patients. The physical examination alone is not sufficient; chest x-rays, blood cell counts, serologic tests for syphilis, urinalyses, and cytological examinations have probably identified more instances of serious disease in supposedly healthy persons than have physical examinations. The specific tests to be used should be determined by careful consideration of a number of factors, including age, sex, occupation, and family history. If any of the tests yields an abnormal result, careful clinical examination and evaluation should lead to the correct diagnosis and provide the basis for successful treatment. Screening tests should be based on automatism wherever possible so as to keep unit costs low while permitting a great increase in the number of tests.

Cytological methods will almost certainly find greater use in the future, and I believe that the biopsy will continue to increase in popularity. Its use in the study of minute bits of tissue obtained by needle puncture will probably increase, whether we as pathologists approve or not.

If the methods for determination of the ketosteroid levels can be simplified, it is likely that they will find a greatly increased use in problems of growth and development, infertility, hypertension, and other "metabolic" disorders.

Automatic equipment will probably revolutionize the practice of clinical pathology. There are now available certain new basic scientific instruments which by adaptation and combination, as in the "AutoAnalyzer," promise an even greater degree of automation than is currently available. Thus a proportioning pump could be joined with a continuous-flow recording colorimeter to increase the speed and accuracy of our hemoglobin level determinations. Modification of Coulter's electronic particle counter might permit its operation as a continuous-flow device in conjunction with an automatic sampler plate and a proportioning pump and thereby make the enumeration of leukocytes and erythrocytes an almost totally automatic process. It even seems possible that the differential blood cell count could be made automatic by the use of fluorescent stains and a television-type scanner, as has been proposed for the screening of cytology smears.

Mechanization will probably permit the clinical pathologist to achieve a degree of accuracy that was previously possible only when tests were performed in triplicate. When that time comes, we can anticipate that our colleagues in clinical research will ask us to perform their tests. They will ask us because potentially we can offer better service than they can develop, and at a much lower cost.

In the small research laboratory everything is in triplicate, especially the costs and the headaches! After the investigator has received his grant, he generally spends at least a month searching for a qualified technical assistant. With her help he then orders the equipment for the laboratory, duplicating several expensive items already available in the clinical laboratory. When the equipment arrives, they spend several weeks in setting up the laboratory in space sorely needed by the clinical pathologist. By the time the laboratory is ready, summer has rolled around and the investigator goes on his vacation. When he gets back, the technical assistant takes some time off. Perhaps after four months of the grant period the team is ready to begin work on patients, but by this time the technician is pregnant or has a better job and so the investigator must start all over again. This harrassment is typical but so unnecessary. I believe that the clinical investigator will, in the future, purchase services from the clinical pathologist to the ultimate advantage of all concerned.

Anticipated Developments in the Teaching of Pathology

Although there is in some circles a move to emphasize the basic science aspect of pathology by having students participate in animal experiments, I suspect that the ultimate change in emphasis will be in the opposite direction, i. e., toward the hospital. After the theories and generalizations of anatomy, biochemistry, physiology, and bacteriology, the student is anxious to learn of disease and of sick people. This can best be done by using the gross and microscopic alterations in the organs and tissues to explain the symptoms and physical signs and roentgenographic changes in the individual patient.

After a student has received instruction in pathological anatomy, oriented toward the patient, I would like to see him spend a brief clerkship in

clinical pathology before beginning his regular ward clerkship. During this preliminary period of about a month, I would assign him cases embodying common problems of clinical and laboratory diagnosis. I would require him to participate in the diagnostic studies in the bacteriology, chemistry, and hematology laboratories, reporting his observations at scheduled conferences conducted by the clinical pathologist.

At the graduate level, I predict that medical residents will be more regularly assigned for training in clinical pathology. Surgical residents have long been offered periods of study in pathological anatomy, and most of them have derived permanent benefit from the experience.

Research Horizons in Pathology

It is likely that studies in cancer will continue to dominate research in experimental anatomic pathology. The techniques of histochemistry and radioisotopes will undoubtedly be used extensively in probing for the secrets of the cell nucleus.

In the field of hematological research, thrombosis will probably receive much study. It seems likely that there are fundamental differences between thrombosis within a blood vessel and clot formation in a test tube and that new research methods will be needed to explore the former. The relationship of thrombosis to elevation of the blood cholesterol level is suggestive in its implications regarding atherosclerosis. (Which comes first, the thrombus or the plaque?)

Near the horizon, but likely to be upon us before we know it, are chemical tests for the diagnosis of nervous and mental diseases. On the one hand, we know that in some patients severe mental illness may be alleviated by chemical "tranquilizers." On the other hand, a clinical syndrome similar to parkinsonism in some cases and to myotonia in others has been noted to follow the use of the tranquilizers in certain instances. These two observations suggest that some psychotic states and neurological disorders may have an essentially chemical basis. If so, it is likely that chemical tests can be devised to aid in their recognition and treatment.

What lies beyond these horizons it is impossible to say. We do know that we have at hand great potential resources for discovery and achievement and for the relief of human suffering.

May the next 100 years reveal to our successors a continual unfolding of truth.

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NATURE OF STAPHYLOCOCCIC INFECTIONS.—Intracellular residence may protect staphylococci from substances in extracellular fluids which ordinarily destroy them. The studies of Tompsett indicate that intracellular staphylococci are protected from antimicrobial drugs present in the surrounding milieu. From 50 to 200 times the amounts of penicillin or streptomycin necessary to kill extracellular staphylococci are required to appreciably affect intracellular staphylococci. . . . It appears clear that this protection cannot be explained by simple failure of antimicrobials to reach the interior of leukocytes. What seems more probable is that staphylococci are metabolically less active within cells and that this sluggishness conditions their susceptibility to antimicrobial drugs. . . . Intracellular survival may also modify the way staphylococci behave within the vascular system of experimental animals. When large numbers of staphylococci are injected into the rabbit blood stream, the majority of microorganisms are removed during the first 10 to 15 minutes by the liver and spleen. Then something happens abruptly. The splanchnic tissues no longer trap staphylococci, and a prolonged bacteremia lasting for hours, indeed for many days, results. . . . This is not the case with bacteria commonly destroyed within phagocytes. . . . It is our current belief that staphylococci surviving within polymorphonuclear leukocytes may play a role in this surprising persistence of microorganisms within the blood stream.—D. E. Rogers, Observations on the Nature of Staphylococcal Infections, *Bulletin of the New York Academy of Medicine*, January, 1959.

PERFUSION TREATMENT OF PATIENTS WITH CANCER

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Perfusion techniques in the treatment of patients with cancer consist in circulating solutions of anticancer drugs through the blood vessels. If the neoplasm is limited to a part that can be isolated, regional perfusion is used; if this is not possible, marrow is first removed from the sternum and iliac crests, total-body perfusion is carried out, and the marrow is reinjected intravenously after the perfusion has been completed. Perfusion methods were used in 145 patients with cancers, 72 of which were carcinomas. There were 56 perfusions of the lower extremity. Perfusion made it possible to attain, in the tumor-bearing area, 15 to 20 times the concentrations obtainable by systemic administration. No specificity of an agent for a given tumor was found, and none of the agents tried was curative. The complications of the treatment in most instances were not serious, but there were eight operative deaths. The best results were obtained in patients with malignant melanoma.

Critical appraisal of the treatment of patients with cancer during the past 25 years leads to the distressing conclusion that, for all its variety, therapy is little more effective now than it was a quarter of a century ago. With some exceptions, about the same number of cures were obtained then as now; for the patient with advanced cancer, death is as relentlessly certain now as then. To be sure, better methods of diagnosis and improved supportive care of the surgical patient have resulted in the treatment of an increased number of patients with localized curable tumors and in a lower operative mortality. Still, in terms of the ability to eradicate human cancer, operation and irradiation are little more effective now than they were formerly.

An awareness of the limitations of existing forms of therapy led to investigation of the treatment of cancer patients with chemical agents. Nitrogen mustard was first employed in the treatment of lymphosarcoma in the mouse about 18 years ago,[1] and in the ensuing years an enormous amount of effort has been devoted to finding effective cancericidal drugs. Yet, once again the fact is inescapable that the patient with advanced cancer, exclusive of cancer of the breast and of the prostate, dies just as surely and with about the same severity of symptoms as he did before the era of chemotherapy.

There are two main reasons for the failure of cancer chemotherapy. In the first place, it has been necessary to search for a cure before the cause of cancer could be found. Second, the toxic side-effects of anticancer drugs which have been developed necessitate the use of doses too small to be curative. It appears that the dilemma created by having to look for "cure before cause" will be resolved in the foreseeable future, and specific drug therapy for cancer will emerge. In the meantime efforts to improve the effectiveness of existing chemotherapeutic drugs must be continued. One way of increasing the effectiveness of an agent is to increase its concentration in the tumor-bearing tissues. Klopp and associates[2] attempted to accomplish this by intra-arterial administration of nitrogen mustard and were able to demonstrate an increased tumoricidal effect. However, it was necessary to use relatively small individual doses to avoid arterial and local tissue injury. The depression of hematopoiesis, while a limiting factor, was not as severe as that after intravenous therapy. Recently we have attempted to develop techniques for administering high concentrations of chemotherapeutic agents in such a way that the toxic effect on the marrow is reduced without impairing the cancericidal effect of the agent. These perfusion techniques have been used in the treatment of patients with cancer for the past two years and the results of this experience are reviewed here.

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Techniques

Techniques of perfusion have been described in detail elsewhere.[3] In general, they are of two types: regional and total-body. In the former an attempt is made to confine the effects of a chemotherapeutic agent to the tumor-bearing area (fig. 1). This technique is applicable to regionally confined but nonresectable neoplasms and includes methods for perfusing the extremities, pelvis, lung, breast, oropharynx, and brain. Total-body perfusion is the term applied to chemotherapy of disseminated cancers for which regional perfusion would be inappropriate.

The techniques of regional perfusion vary somewhat, depending on the area to be treated, although the underlying principles are the same. The artery and vein supplying the part or region are occluded proximally, cannulated in a distal direction, and connected to an extracorporeal circuit consisting of arterial and venous pumps and a bubble oxygenator. In perfusing the extremities a tourniquet is applied, proximal to the sites of cannulation, thus effectively, if not completely, isolating the perfused

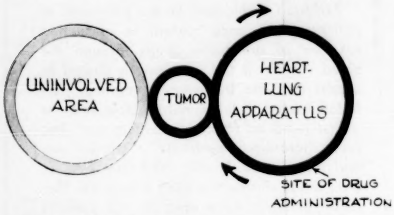

Fig. 1.—Schematic diagram of principle underlying regional perfusion in treatment of human cancer.

part from the systemic circulation. In the treatment of lesions within the pelvis, tourniquets are applied to the upper part of the thighs and the patient is placed in such a position that the lower half of the body is dependent. Perfusion of the lungs requires the use of two extracorporeal circuits, one for the heart and lungs and one for the systemic circulation. In perfusion of the breast, oropharynx, and brain the chemotherapeutic agent is less well confined to the tumor-bearing area than in perfusion of other areas. When a tumor is confined to the foot or lower portion of the leg, perfusion of the extremity from the knee down is accomplished through the lower superficial femoral artery and vein. For lesions on the thigh, "hindquarter" perfusion is done through the external iliac or common femoral vessels. Similarly, for lesions of the hand and wrist, perfusion of the forearm is carried out, usually through the brachial artery and vein. For lesions about the arm and axilla the axillary vessels just below the clavicle are cannulated; for lesions of the shoulder, the subclavian artery and vein are used. For tumors of the oropharynx perfusion is carried out through the external carotid artery and the facial and external jugular vein of the ipsilateral side, and for lesions of the brain the internal carotid artery and internal jugular vein are used.

Total-body perfusion consists in the removal of marrow from the sternum and iliac crests immediately prior to treatment. Catheters are then passed into the thoracic aorta and inferior vena cava by way of the common femoral artery and vein, respectively, and perfusion is begun. When perfusion is completed the marrow is returned to the patient by intravenous infusion.

Chemotherapeutic Agents

At the beginning of this study, four chemotherapeutic agents were used in the treatment of human cancers. These were the alkylating agents nitrogen mustard (HN_2), phenylalanine mustard (PAM), triethylenemelamine (TEM), and triethylenethiophosphoramide (thio-TEPA or TSPA). Later, actinomycin-D (Act.-D) and 5-fluorouracil (5-FU) became available. Actinomycin-D is an antibiotic that acts primarily on the cytoplasm of the cell, in contrast to the alkylating agents, which are primarily nuclear toxins; 5-fluorouracil is an antimetabolite, producing metabolic block at sites essential to growth of the cell. More recently a combination antimetabolite and alkylating agent (AB 100) has been employed in several cases.

The amounts of these agents that can be administered to various regions depend on several factors, namely, the size of the perfused area, the completeness of isolation, the duration of action of the chemotherapeutic agent, and whether the patient has received prior chemical therapy or irradiation (table 1). For instance, nitrogen mustard and 5-fluorouracil have a short duration of action and may be used in relatively large doses when the perfused part can be isolated. Thus, for the lower extremity, twice the usual systemic dose can be safely administered. In perfusion of the upper extremity, however, the dose of these agents must be reduced because of the small mass of the part. On the other hand, phenylalanine mustard and TSPA remain active for at least several hours. Thus, irrespective of the area perfused, the usual systemic dose should not be exceeded. When an extremity or the pelvis is perfused with these agents, an attempt is made to remove any residual amount

TABLE 1.—*Schedule of Dosage in Milligrams per Kilogram of Body Weight of Five Drugs Used in Perfusion Treatment of Cancer*

Agent	Region				
	Pelvis	Lower Extremity	Upper Extremity	Oropharynx and Brain	Total Body
HN_2	0.8	0.8	0.4	0.2-0.3	0.8-1.2
PAM	1.5	1.5	1.0		
TSPA	1.0	0.8	0.6	0.6-0.8	
Act. D	0.05	0.05	0.035		
5-FU	20.0	20.0	15.0		
AB-100	3.5				

of the drug at the end of perfusion by draining the venous system and infusing dextran through the arterial line. Even this maneuver does not entirely eliminate the depressive effects of phenylalanine mustard and TSPA on the hematopoietic system. When chemotherapy or irradiation has been employed in the recent past, the amount of an agent administered by perfusion should be reduced.

In some instances it may be desirable to combine two or more chemotherapeutic agents. The dose of each will vary, depending on the degree of isola-

lation of the tumor-bearing area. For perfusion of the extremities, in a case in which isolation is relatively complete, we have used a dose of each agent roughly comparable to that employed when the agent is used alone.

The choice of a chemotherapeutic agent for a given tumor has been largely arbitrary, although based somewhat on our own experience and that of others. In general, phenylalanine mustard and TSPA have been used in the treatment of malignant melanoma and some sarcomas. Nitrogen mustard has been employed in the treatment of rhabdomyosarcoma and carcinoma of the lung, gastrointestinal tract, and breast. TSPA has been used in the treatment of ovarian carcinoma and of neural tumors. Actinomycin-D, 5-fluorouracil, and AB-100 have been used singly or in combination with the alkylating agents in the treatment of adenocarcinoma and some sarcomas.

In administering an anticancer drug several factors must be considered. The available agents, irrespective of their mode of action, are most effective if brought in contact with the neoplastic cell at about the time of mitotic division. Thus, the longer an active agent is in contact with a tumor, the greater the number of cells affected during this vulnerable period. At the same time, the bubble oxygenator becomes less efficient and produces damage to the cellular elements of the blood when it is operated in excess of one and one-half hours. This has limited the length of perfusion. Finally, with perfusion techniques, drug administration is intra-arterial, in that the agent is injected into the arterial line just proximal to the arterial pump. Thus, if a large dose of a vesicant agent such as nitrogen mustard is employed, care must be taken not to administer it in a single injection, since this has been shown experimentally to produce arterial injury and thrombosis.

TABLE 2.—*Summary of Cases of 145 Patients Treated by Perfusion*

Type of Tumor	No. of Cases	No. of Perfusions
Carcinoma	72	74
Melanoma	40	50
Sarcoma	28	33
Glioblastoma	5	5
Total	145	162

Methods of administering chemotherapeutic agents have varied. The total dose of nitrogen mustard or 5-fluorouracil is divided into four or five equal portions, and these are administered three to five minutes apart. PAM and TSPA, having an extended duration of action, may be administered in a single dose or in two equal doses, 10 to 15 minutes apart. When two agents are used in combination, each one is divided into two equal doses and these are given alternately at five-to-eight-minute intervals.

Analysis of Cases

Since June, 1957, 145 patients with cancer have been treated by perfusion methods. The youngest patient was 11 years of age while the oldest was 88, the average age for the entire series being 50 years. There were 69 male and 76 female patients.

Among the 145 patients there were 40 with malignant melanoma, 28 with sarcoma, 72 with carcinoma, and 5 with glial tumors (table 2). Perfusion

TABLE 3.—*Summary of Results in 120 Patients Treated by Perfusion*

Tumor	Therapy*	Recurrent After Response: Quiescent	Recurrent After Response: No Effect	Died as Result of†: Operation	Died as Result of†: Chemotherapy	Died as Result of†: Tumor
Melanoma	A	3	1			
	P	21	6	2	1	2
Sarcoma	A	5				
	P	4	10	6		8
Carcinoma	A	6			1	
	P	14	10	22	6	16
Glioblastoma	A					
	P	2				
Totals		55 (46%)	27 (22%)	30 (25%)	8 (7%)	2	27

* A—adjuvant therapy; P—palliative therapy.
† With exception of operative deaths, patients who died are classified according to response to treatment prior to death.

was performed once in 133 patients, twice in 9 patients, three times in 1, and 2 patients were perfused four times, for a total of 162 perfusions in the entire group. Most of these patients had cancer that was recurrent or metastatic to the extent that cure could not reasonably be expected from any type of therapy, and in these treatment has been classified as palliative. There were 128 in this category. In 17 cases perfusion was carried out as an adjunct to surgical removal of a localized primary tumor.

There were 56 perfusions of the lower extremity, including 6 "hindquarter" perfusions; 22 of the upper extremity, including 7 "forequarter" perfusions; 26 of the pelvis; and 13 of the breast. The lungs were perfused three times, the oropharynx four times, and the brain five times. Total-body perfusion was carried out in 33 cases.

Of the 145 patients, 25 were treated too recently to permit any evaluation of results. Of the remaining 120 there were 33 with malignant melanoma (table 3), and in 4 perfusion was carried out as an adjuvant to surgical excision of the primary lesion. In three of these there has been no reappearance of the tumor after treatment, but in one case recurrence is evident.

There were 29 patients with malignant melanoma who were treated for palliation of recurrent or far-advanced tumors (table 3). Among these, the tumor remained quiescent in 21 and in 6 there was a significant temporary response of the tumor to treatment but the lesions subsequently recurred. In two patients treatment had no effect.

There were five deaths among patients with melanoma, one of which was operative, two of which resulted from widespread metastases, and two of which were due to an excessive dose of phenylalanine mustard.

Among the patients treated for sarcoma, 25 are suitable for evaluation (table 3). In five of these perfusion was done in conjunction with surgical excision of the primary lesion, and in all the disease has remained quiescent. There have been no deaths in this group. Twenty patients with sarcoma were given palliative treatment and among this group there are four in whom the tumor appears to be quiescent. There were 10 patients in whom the tumor showed temporary regression, while 6 patients failed to show any improvement. Eight patients died after treatment, all as a result of their disease.

Of the patients with carcinoma, perfusion was performed in conjunction with surgical excision of the primary lesion in seven, and six of these patients have remained well (table 3). In the 53 cases in which treatment was palliative, 14 patients have shown a significant response in that the tumor appears to be quiescent. In 10 patients an immediate regression of the tumor occurred but there was subsequent recurrence, and in 22 perfusion apparently had no effect on the growth of the neoplasm.

There have been 23 deaths among patients with carcinoma, 7 of which were operative (table 3). Among these was one patient with recurrent metastatic ovarian carcinoma in whom pelvic perfusion was performed in spite of the presence of an anti-e factor that prevented satisfactory crossmatching with blood donors. This patient developed hemolytic anemia as a result of the blood dyscrasia, not of the chemotherapeutic agent, and died on the 10th day after operation. There were two patients with carcinoma of the lung who died soon after perfusion. In one, death was due to necrosis of a large cerebral metastasis, with cerebral edema, and in the other it was due to hemorrhage from the operative site. Of the 23 patients who died, 16 left the hospital after treatment but died from their disease.

Perfusion was carried out in five patients with glioblastoma multiforme, but three were treated too recently to be included in evaluation of results (table 3). In all of these craniotomy and decompression had been performed previously. Four of these patients are alive and improved after treatment and one died of the disease after a period of slight clinical improvement.

In summary, of 120 patients treated by perfusion 55 (46%) have shown significant improvement, in that the cancer appears to be quiescent. In 27 (22%), temporary regression of the tumor occurred but this was followed by recurrent growth. Thirty patients (25%) showed no response to treatment. There have been 36 deaths, 8 of which were operative. Two patients died with severe marrow depression; one of these deaths occurred in the late postoperative period and is classified as both an operative and a chemotherapeutic fatality. The remaining 27 died of their disease.

Complications

Complications of the perfusion treatment of human cancer have resulted from the surgical procedure itself and from the chemotherapeutic agents. The commonest surgical complication has been edema of the involved extremity. A majority of patients who have been treated for tumors of the extremities have had prior regional node dissection which was followed by moderate swelling of the limb. After perfusion edema of the extremity has increased immediately, but the limb has returned to its preperfusion size in two to three weeks. In a case in which regional node dissection has been accomplished in conjunction with perfusion, delayed healing of the skin flaps has been observed, but it is questionable whether this poor wound healing differs in any way from that often encountered after node dissection.

Since a major vein is cannulated and subsequently repaired, venous thrombosis is a potential complication in every instance. However, in this series it has been encountered only twice and in one of these cases thrombosis of the common femoral vein had been present prior to perfusion. At operation thrombectomy was performed, perfusion was carried out, and the vein was reconstituted. Subsequently venous thrombosis recurred and was followed by pulmonary infarction. In another case, perfusion of the upper extremity was followed by axillary vein thrombosis and massive edema of the extremity. In 12 patients in whom a second, third, or fourth perfusion has been performed, thrombosis of the vein has not been encountered in a single instance, nor has arterial thrombosis been a problem. In no instance has there been any difficulty in restoring arterial continuity and peripheral pulses distal to the site of arterial cannulation.

Complications resulting from administration of the chemical agents have consisted in damage to soft tissues of the perfused area, depression of hematopoiesis, and absorption of toxic products from massive destruction of neoplastic tissue. Injury to normal soft tissue is manifested primarily by erythema of the skin over the perfused region. This gradually changes to a brown discoloration which persists for several weeks. These changes are similar in many respects to those observed after irradiation. In some instances edema of skeletal muscle has been observed and is accompanied by moderate

to severe tenderness in the involved muscle groups. In the lower extremity, the gastrocnemius muscle is most often affected. This involvement usually runs its course in about three to four weeks. These changes are most severe after perfusion of an extremity and are usually controlled with elastic compression bandages and elevation of the part. When the skin and muscle changes are moderately severe, administration of prednisolone has been effective in relieving these symptoms.

Peripheral nerve injury has been observed after perfusion of the upper extremity in two cases. In one of these the median nerve was involved while in the other there was radial nerve palsy. It is not clear whether nerve injury resulted from the chemotherapeutic agent or from the tourniquet. In both cases there has been a gradual return of function.

Interference with hematopoiesis is manifested by a reduction in the leukocyte and platelet counts (fig. 2). These usually appear about five to seven days after perfusion and persist for four to five days, when recovery begins. In many instances a significant reduction in erythrocyte content has been observed also. This becomes apparent one or two days after perfusion and is probably due to hemolysis, although evidence for this is not always present. In one case a large dose of nitrogen mustard was used for pelvic perfusion and severe hemolysis occurred within 48 hours, evidenced by a significant reduction in the erythrocyte count and elevation of the serum bilirubin content. Hematopoietic changes are observed whenever regional confinement of the agent is inadequate, and their severity depends on the amount of agent used. In most instances leukocyte depression has been mild, although in 19% of cases the leukocyte count has dropped below 1,000 cells per cubic millimeter. In spite of their severity these changes usually respond to transfusions of fresh whole blood, steroid therapy, and administration of antibiotics. In three instances drug-induced leukopenia led to the patient's death.

Comment

This experience in treating 145 patients with cancer with chemotherapeutic agents administered by perfusion has made possible certain observations which appear to be pertinent to the therapy of tumors in human beings. First, and perhaps most important, is the conclusion that under conditions imposed by these methods, none of the anticancer drugs presently available is curative. Although it is possible, by regional perfusion, to achieve concentrations of a chemotherapeutic agent in a tumor-bearing area 15 to 20 times those obtained with systemic administration, in no instance has the response to a neoplasm been indicative of true specificity. To be sure, striking resolution of malignant lesions has occurred after treatment, but in no instance has this response matched that observed, for example, when a hemolytic streptococcic infection is treated with penicillin. It must be admitted that, by the methods described here, a chemotherapeutic agent in high concentration is in contact with the neoplasm for a relatively short time. This is probably inadequate for its maximum effects to be realized. Experiments to develop methods for significantly prolonging the period of perfusion are now in progress.

It is also evident from this study that there is little specificity of an agent for a given tumor. Thus, phenylalanine mustard may produce rapid resolution of metastatic melanoma in one case while in another there will be no response whatsoever, or two or three agents may be employed in successive perfusions before an effective one is found. For example, a patient with subcutaneous metastatic melanoma of the lower extremity was treated by perfusion on one occasion with phenylalanine mustard and subsequently with a combination of

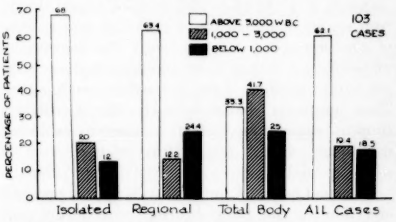

Fig. 2.—Leukocyte depression after perfusion.

phenylalanine mustard and TSPA. There was little response of the lesions to these agents and within a short time they began to grow rapidly. Finally, perfusion with nitrogen mustard was carried out and an interesting and gratifying phenomenon ensued. Within three or four days the skin over the subcutaneous lesions became red and edematous, and within two or three weeks each metastasis, with its overlying skin, became necrotic and sloughed. In contrast, in the first patient treated for melanoma by perfusion with phenylalanine mustard, the lesions began to regress within a few weeks and eventually disappeared.

Depression of hematopoiesis after perfusion with a long-acting agent is a complication of considerable importance. For instance, a significant leukopenia developed after limb perfusion with phenylalanine mustard and TSPA in about 10% of patients, although most of the agent was confined to the perfused area and attempts were made to remove residual amounts of the agent at the end of treatment. This implies that some of the drug remains in the

tissues until isolation of the part is ended, when systemic distribution and marrow injury occur. In addition, it has been suggested recently that absorption of the products of drug-induced tumor necrosis may have a depressive effect on hematopoiesis.[4] In any event, cancer chemotherapy by perfusion requires the same judicious use of an agent as does systemic administration.

As indicated earlier, the initial choice of an agent is somewhat arbitrary. Obviously, a "sensitivity test" is sorely needed. We are now using a test which depends on vital stains to determine the viability of neoplastic cells after their exposure to chemotherapeutic agents, and, while this method has been used in the selection of an agent in about 15 cases, there is no evidence that it is specific.

Certain factors related to perfusion itself are of importance to successful treatment. There are some indications that the tissue should be maintained at or near normal temperature for maximum effectiveness of the cancericidal drug. When an oxygenator is used the temperature of the blood is reduced as much as 10 to 12 F (5.5 to 6.6 C), and this in turn results in significant reduction of temperature of the perfused part. Apparently the decrease in metabolism resulting from cooling interferes with the cytotoxic effect of the chemotherapeutic agent. Thus, measures should be taken to prevent this drop in temperature. In fact, we are now exploring the effects of high temperature on the action of cancericidal drugs.

A second factor of importance is that of pressure and flow in the tumor-bearing area during perfusion. At high rates of flow there appears to be patchy distribution of the perfusate, and at pressures in excess of the systemic systolic pressure, leakage from the perfusion circuit becomes excessive. Therefore, it is desirable to measure blood flow and pressure continuously during perfusion.

The changes which occur in a malignant neoplasm after treatment with a cancericidal agent administered by perfusion are varied and have been studied best in patients with melanoma. Metastases of malignant melanoma show several types of response. Subcutaneous lesions and metastases to regional nodes usually begin to decrease in size within three to four days after treatment and may disappear completely. Less often an intense, inflammatory reaction develops about the subcutaneous nodule and involves the overlying skin. In a patient mentioned earlier these areas sloughed completely.

Cutaneous melanoma usually responds in one of two ways. Small lesions, whether melanotic or amelanotic, become black, flattened, and dried. Often these tumors disappear entirely, leaving a residual freckle. Large cutaneous metastases become hemorrhagic within two to three days after perfusion and go on to ulceration and perhaps to complete disappearance.

Bulky metastatic melanoma may become reduced in size, as a result of tumor necrosis, after perfusion. This seems to produce a peripheral retraction of the tumor so that its involvement of adjacent tissues is diminished. Similar regressive changes have been observed in patients with all of the types of cancer treated. In those with certain sarcomas temporary reduction in size has been particularly striking.

The mechanisms for development of these changes, particularly those observed to occur in patients with melanoma, require further investigation. Certainly, in some instances, it appears that the host-tumor relationship is disturbed sufficiently so that resistance factors gain control of the neoplasm. In some the neoplastic cells appear to lose their ability to reproduce themselves, and this may be the principal factor in temporary control of the tumor.

The place of regional chemotherapy in the treatment of human cancer remains to be determined. It is entirely possible that the desire for an agent as effective as aspirin and as free from toxic side-effects will be realized. Such a development would, of course, revolutionize the treatment of patients with cancer. On the other hand, assuming that the agents which are developed, while perhaps more effective therapeutically, will have toxic properties similar to those now in use, regional perfusion may be useful. From this series, it is clearly evident that regionally confined metastatic melanoma is significantly affected by the perfusion treatment; in fact, it is safe perhaps to conclude that it is the most effective therapy for patients with this disease in its recurrent or metastatic form. Its value as an adjunct to conventional surgical methods remains to be determined. At the other extreme the use of chemotherapeutic agents administered by perfusion for the treatment of patients with gastrointestinal carcinoma has been essentially without effect. Somewhat better response has been observed in the treatment of patients with carcinoma of the genitourinary tract, lung, and breast. While in no instance has an advanced lesion in these areas been arrested, significant palliation has been afforded in some cases and in others a nonresectable lesion has been converted to a resectable one. Furthermore, in almost every patient with pain resulting from far-advanced cancer, significant temporary relief of pain has been observed after treatment. With the agents now available, it is too much to expect that bulky tumors will be eradicated by chemotherapy, irrespective of the concentration of the agent and method of admin-

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istration; yet it has been observed in this series that large, solid tumors shrink in size and undergo a considerable amount of necrosis. In the case of bulky lesions which are regionally confined, it is possible to induce peripheral necrosis and shrinkage of the lesion, thus making excision of the tumor feasible. In this way large, fungating, ulcerating lesions are removed and the patient may be rehabilitated, even though cure is not possible. For example, lower extremity perfusion was performed for metastatic melanomas in a patient who had been bedridden for two years. One of the lesions on the anterior part of the thigh weighed about 15 lb. and was ulcerating and foul. After perfusion and almost complete necrosis of this large lesion the residual base was excised and the area covered with a skin graft. Perfusion was performed again subsequently and the patient is now ambulant and relatively free of symptoms. The possibility that other lesions may appear later detracts in no way from the successful palliation achieved in this case.

The ease and safety with which perfusion can be repeated is gratifying. Lacking a "sensitivity test" it may be necessary to resort to trial of several agents administered at separate operations. In addition, retreatment of a responsive tumor is feasible, thereby increasing the opportunity for control of the lesion.

Insufficient experience with total-body perfusion has accumulated for proper evaluation. It is not certain that marrow replacement is necessary with the doses of nitrogen mustard used in this study. This and other aspects of total-body perfusion require investigation.

The use of perfusion techniques in the treatment of neural tumors may prove to be of importance. Although our experience with the treatment of tumors of this type is limited, Woodhall [5] and others are also investigating techniques for perfusing the brain, and an early evaluation of the effectiveness of this form of therapy may be possible.

Summary

Cancer chemotherapy with cytotoxic agents has the limitation of systemic toxicity, when large doses are used. Perfusion treatment is an attempt to diminish the toxic side-effects while permitting the use of larger doses of the cancericidal drugs. Perfusion techniques are of two types, regional and total-body. In the former, the effects of the drug are largely confined to the tumor-bearing area. In the latter, whole-body distribution of the agent occurs, but an attempt is made to minimize hematopoietic changes by autologous marrow transplantation. Techniques have been developed for regional perfusion of the extremities, pelvis, lungs, breast, oropharynx, and brain. The chemotherapeutic agents employed are nitrogen mustard, phenylalanine mustard, thio-TEPA, actinomycin-D, 5-fluorouracil, and a combined antimetabolite and alkylating agent (AB-100). Dosage of these agents varies with the area perfused, completeness of isolation, duration of action of the drug, and whether the patient has been given prior drug or x-ray therapy.

In the series reported, in 145 patients perfusion was performed 162 times for the treatment of cancer. There were 40 with malignant melanoma, 28 with sarcoma, 72 with carcinoma, and 4 with glioblastoma. Results of treatment have been evaluated in 120 cases. In 17 of the patients treatment was adjunctive to surgical excision of a primary tumor, and in 103 it was attempted for palliation of far-advanced cancer. In 55 the lesions are quiescent, in 27 there has been temporary regression of the tumor, followed by recurrent growth, and in 30 perfusion was without effect. There were eight operative deaths. Complications consisted of edema and discoloration of the perfused area and depression of hematopoiesis. In most instances these complications were not serious and responded promptly to therapy. Regional perfusion for malignant melanoma appears to be effective in the treatment of patients with recurrent or metastatic lesions. The value of perfusion in the treatment of patients with other types of tumors is not yet clear.

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MYOPATHY AND HYPERCALCEMIA OCCURRING WITH CARCINOMA OF THE KIDNEY

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and
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In this case of a 63-year-old man the essential complaint during the first three months of illness was muscular weakness, affecting especially the legs and progressing to complete disability. Later symptoms led to surgical removal of the right kidney and diagnosis of clear-cell carcinoma. The nephrectomy was followed by improvement in neuromuscular status until muscle strength had returned to almost normal. Deep reflexes in the legs did not return, and biopsy of the quadriceps femoris muscle revealed extensive atrophy. Hypercalcemia was detected before operation and subsided thereafter; its time-relation to other blood-chemical findings, to the neuromuscular disturbance, to osteoblastic activity manifested in the bones, and to the ultimate appearance of masses in both lungs suggests that calcium played a central role in the symptomatology of this patient.

The occurrence of neuromuscular diseases in association with malignant tumors has become a well-recognized entity in the past 10 years. A few reports [1] of neurological disorders accompanying carcinoma appeared many years ago. In 1948 Denny-Brown [2] reported two cases of peripheral neuropathy associated with carcinoma of the lung, and interest was reawakened in this syndrome. Later, the excellent papers of Brain, Henson, and others [3] defined quite well the clinical and pathological characteristics of the varied neurological and muscular disorders which have appeared in association with carcinoma.

In most of the reported cases,[3] the primary neoplasm originated in the lungs. The syndrome has also been reported with carcinoma of the prostate, ovary, rectum, and breast and in cases where the primary site of malignancy could not be determined.[3b] To our knowledge no previous report has appeared in which neuromuscular disease was associated with carcinoma of the kidney. The present case report also appears to be noteworthy because of the presence of hypercalcemia and hypophosphatemia preoperatively.

Report of a Case

A 63-year-old man was admitted to the Durham Veterans Administration Hospital on July 17, 1958, because of severe generalized muscle weakness of four months' duration. The patient had been perfectly well until January, 1958, when he began to notice progressive weakness in the legs on attempting to arise from a sitting position or on ascending steps. Slapping gait with drop foot and failure of muscle strength in the arms appeared shortly thereafter. The weakness was primarily in the proximal muscles, but weakness of handgrip was present also. Three months after the onset of progressive muscle weakness the patient developed colicky pain in the right flank which was thought to be due to passage of a renal calculus. The same type of flank pain recurred one month later, and the patient was hospitalized elsewhere for evaluation. He remained bedfast and became unable to raise his arms sufficiently to feed himself. He was transferred to the Durham Veterans Administration Hospital on July 17, 1958. Throughout the course of his illness he had lost 44 lb. (20 kg.).

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On physical examination, the patient was a euphoric 63-year-old man, with blood pressure 130/70 mm. Hg, pulse rate 76 per minute, and temperature 98.6 F (37 C). The skin showed bilateral palmar erythema. Extreme weakness and wasting of the muscles of the extremities was present. The patient was unable to sit unassisted or to extend his arms above the bed. The handgrip was weak but not as markedly reduced in strength as the proximal muscle power. The deep tendon reflexes were normal in the arms and were totally absent in the legs. The cremasteric reflexes were absent. Plantar response was downward on the right and of withdrawal character on the left. Sensory examination showed no deficit to pinprick, position, or vibration. Tingling dysesthesia to sensory stimulation of the feet was noted by one observer. The remainder of the physical examination was noncontributory.

Initial laboratory data showed the hemoglobin level to be 12.0 Gm.% and white blood cell count 9,800 per cubic millimeter. The urinalysis showed a faint trace of protein and 0 to 3 white blood cells per high-power field. The blood urea nitrogen level was 20 mg.%. Serum sodium, chloride, and potassium levels and carbon dioxide–combining

power value were normal. The alkaline phosphatase level was 2.4 Bodansky units, and the acid phosphatase level was 0.1 King-Armstrong units. Eight days after the patient's admission the serum calcium level was 11.4 and the serum phosphorus level 2.0 mg.%. (Subsequent values are shown in the table.)

Laboratory Data in Patient with Myopathy and Hypercalcemia Occurring with Carcinoma of the Kidney

Date	Serum Calcium Level, Mg. %	Serum Phosphorus Level, Mg. %	Alkaline Phosphatase Level, Bodansky Units	Acid Phosphatase Level, King-Armstrong Units	Blood Urea Nitrogen Level, Mg. %
7/17	..	..	..	..	20
7/21	..	29	24	..	..
7/23	..	3.1	..	0.1	..
7/25	11.4	2.0	..	..	..
8/3	11.3	..	..	..	..
8/4	..	2.8	2.5	0.3	..
8/8*	..	..	..	..	20
8/9	8.8	3.2	..	..	..
8/13	8.8	3.0	1.3	0.1	11.5
8/22	8.6	..	..	..	..
12/12	10.6	..	20†	..	19.5

* Nephrectomy was performed on 8/6.
† King-Armstrong units (normal values = 4 to 12 units).

A roentgenogram of the chest showed no abnormality. A film of the pelvis showed considerable increase in density of the left innominate bone with preservation of the trabecular pattern, suggesting osteitis deformans (Paget's disease). Films of the skull, spine, and femurs showed no lesions. Intravenous pyelography showed distortion of the upper pole of the right kidney (fig. 1).

Lumbar puncture yielded clear spinal fluid under normal pressure. No cells were present in the fluid, and the total protein level was 24 mg.%. The spinal fluid test and blood serologic test for syphilis gave negative results. A needle biopsy specimen of the prostate showed benign hyperplasia of the gland. Bone biopsy specimens from the left ilium showed changes compatible with osteitis deformans and no evidence of metastatic tumor. Muscle biopsy specimens from the right quadriceps femoris showed marked atrophy of individual muscle fibers with areas of fibrinoid degeneration of the sarcoplasm. Prominent infiltration of the muscle tissue by chronic inflammatory cells was present, and the histological architecture was almost totally destroyed (fig. 2).

A right nephrectomy was performed three weeks after admission of the patient. Pathological examination showed replacement of the upper one-half of the kidney by a partially necrotic gray tumor measuring 10 cm. in diameter (fig. 3). Histologically the tumor was a typical clear-cell carcinoma of the kidney (fig. 4).

Postoperatively the patient showed rapid recovery of strength and was able to sit up unassisted one week after the operation. He could walk quite well with slight support from a cane three weeks after the operation. When he returned for reevaluation four and one-half months after operation, he appeared quite well and had gained 28 lb. (12.7 kg.). The general physical examination was not remarkable. Muscle strength showed return to an almost normal level in all groups. His gait was erect and hand strength was good. The deep tendon reflexes were still absent in the legs and minimal decrease to vibratory sense was present in the right foot. Sensation for pinprick and light touch was normal.

The hemogram and urinalysis showed normal findings. The serum calcium level was 10.6 mg.%, alkaline phosphatase level 20 King-Armstrong units, and blood urea nitrogen level 19.5 mg.%. A chest roentgenogram showed the presence of a density at the left hilus, measuring 3 by 5 cm., and a smaller density in the right lung field. Both of these lesions had appeared since the previous admission and were thought almost certainly to be

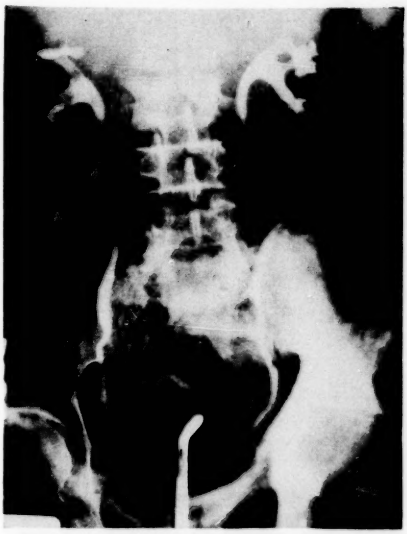

Fig. 1.—Retrograde pyelogram showing filling defect at superior pole of right kidney and osteoblastic activity in left innominate bone.

metastases. A muscle biopsy specimen from the right quadriceps femoris showed atrophy of the muscle fibers. No fibrinoid degeneration was present in this specimen (fig. 5).

Comment

A multiplicity of neurological and muscular disorders have been described in accompaniment with carcinoma. The more common patterns of

neurological disturbance have fallen into four groups [3e]: (1) cortical and cerebellar degeneration in which ataxia, Babinski responses, adventitious movements, diplopia, and nystagmus have been the predominant findings; (2) mixed motor and sensory syndromes, with marked loss of muscle substance, weakness, decrease of deep tendon reflexes, and loss of position and vibration sense; (3) virtually pure sensory neuropathy; and (4) pure myopathy.

Our patient appeared to possess a predominantly myopathic illness. Complete absence of the deep tendon reflexes in the legs and absence of the cremasteric reflex persisted after good recovery of muscle strength had taken place, suggesting that there was also a neuropathic component to the illness.

Autopsy studies in the patients reported in the literature have shown multiple degenerative lesions in the cerebellum, medulla, dorsal root ganglions,

Fig. 2.—Biopsy specimen of quadriceps femoris muscle prior to nephrectomy showing complete loss of muscle architecture, fibrosis, and chronic inflammatory cell infiltration. Single markedly degenerated muscle fiber is present in center of picture (× 69).

and motor cells of the spinal cord.[4] In the patients with pure myopathy, severe degenerative changes of nonspecific nature have been found in the involved muscles.[3e]

The course of these neurological and myopathic illnesses has been quite unpredictable in most cases. Occasional patients have shown improvement after removal of the primary tumor, but in most instances the neurological symptoms have pursued a course independent of the progress of the malignancy. Quite often the neurological symptoms have shown spontaneous improvement at a time when the patient was entering a terminal phase of carcinomatous cachexia.[4]

Fig. 3.—Section of right kidney showing replacement of upper pole by carcinoma.

Speculation has arisen in regard to the pathogenesis of these disorders of the nervous system. Possible etiological factors which have been mentioned include production of a neurotoxic substance by the tumors, autosensitization to tumor protein, and nutritional deficiency due to the presence of a malignant tumor. Investigation [3] has yielded no convincing support for any of these opinions as yet.

The relationship of myopathy to the purely neurological syndromes has been a source of debate. Adams and associates [5] continue to look on the myopathic form as a type of chronic polymyositis. Brain and Henson [3b] have been impressed by the marked diminution of deep tendon reflexes and superficial reflexes and believe that the evidence is sufficient to suggest that the myopathy represents a neuromuscular disorder.

The second remarkable feature of the case reported here was the presence of hypercalcemia prior to operation in the absence of recognizable metastases to the bone. Serum calcium levels of 11.3 and 11.4 mg.% were encountered before operation. Five days after operation the serum calcium level had fallen to 8.8 mg.%. Serum phosphorus levels were low prior to operation and remained at the lower limit of normal after operation. Alkaline and acid phosphatase determinations were normal at the time of operation, but, on reevaluation four and one-half months after operation, the alkaline phosphatase level had risen to 20 King-Armstrong units.

The occurrence of hypercalcemia in association with malignant tumors has been reported previously. Plimpton and Gellhorn [6] described 10 cases

of hypercalcemia accompanying malignant tumors in which no major bony metastases were present. Four of these patients had carcinoma of the kidney (three of the clear-cell type and one of unspecified type). Only 3 of the 10 patients were in an

Fig. 4.—Histological section of renal tumor. Typical clear-cell carcinoma pattern is present. Necrosis of tumor with infiltration by polymorphonuclear cells is shown.

operable state at the time they came under observation. Two of the operable patients had carcinoma of the kidney, and in both the serum calcium level rapidly fell to normal after operation. The third patient, with adenocarcinoma of the ovary, showed a prompt fall in the calcium level after operation, but the hypercalcemia reappeared when local recurrence of the tumor developed. Our patient was similar to these patients in that his serum calcium level fell to normal five days after operation. Four and one-half months later, the serum calcium level was still normal though evidence of metastases in the lungs had appeared. At that time the serum alkaline phosphatase level had risen to 20 King-Armstrong units.

The precise etiology of hypercalcemia accompanying malignant tumors without bone involvement has not been defined.[7] Thomas and associates[7a] showed that the characteristic findings in this syndrome are hypercalcemia of variable degree, hypophosphatemia, and decreased tubular reabsorption of phosphorus. The response of their patients to corticosteroid administration was found to be quite inconsistent, and these workers concluded that the corticosteroid test was of little value in distinguishing the hypercalcemia of malignant disease from true hyperparathyroidism. Histological examination of the parathyroid glands in patients with elevated blood calcium levels and malignant tumors has been unrevealing for the most part, though mild hyperplasia of these glands was seen in one of the reported cases.[8] Elucidation of the origin of hypercalcemia in malignancy must await further study.

In our patient the possibility exists that the entire picture of severe muscle weakness and wasting was due solely to the presence of hypercalcemia. In hyperparathyroidism, marked hypercalcemia may be associated with considerable impairment of muscle strength[9]; in the experimental animal, hypercalcemia has been found to be accompanied by frank necrosis of muscle fibers.[10] In both of these situations the recorded blood calcium values were considerably higher than the ones present in our patient. Accordingly, it seems most unlikely that the modest degree of hypercalcemia seen in this case was sufficient to explain the profound degree of muscle weakness and degeneration.

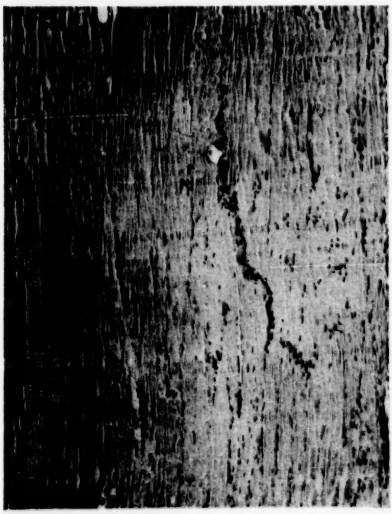

Fig. 5.—Biopsy specimen of quadriceps femoris muscle after nephrectomy showing atrophy of muscle and loss of striations (× 69).

Interpretation of the findings in this patient is further complicated by the presence of osteoblastic activity in the pelvic bones. The roentgenogram and bone biopsy specimen of this lesion showed characteristics of osteitis deformans. Since operative removal of the tumor was followed by prompt

fall in the blood calcium level, we believe that the relationship of tumor to hypercalcemia is fairly clear. It seems reasonable to assume that osteitis deformans was of little importance in this relationship.

Summary

Myopathy and hypercalcemia occurred in a patient with clear-cell carcinoma of the kidney. Progressive generalized skeletal muscle weakness preceded the appearance of hematuria by three months. After operative removal of the renal tumor the patient showed remarkable improvement of muscle strength and the blood calcium levels returned to normal. The patient was asymptomatic four and one-half months after operation, although the chest roentgenogram showed the appearance of masses in both lung fields since the previous admission.

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CLINICAL DIAGNOSIS OF TRACHEAL ADENOMA (CYLINDROMA)

REPORT OF A CASE

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The presenting symptoms in patients with tracheal tumors may be those commonly associated with bronchial asthma. Such a clinical picture is illustrated in the following case report.

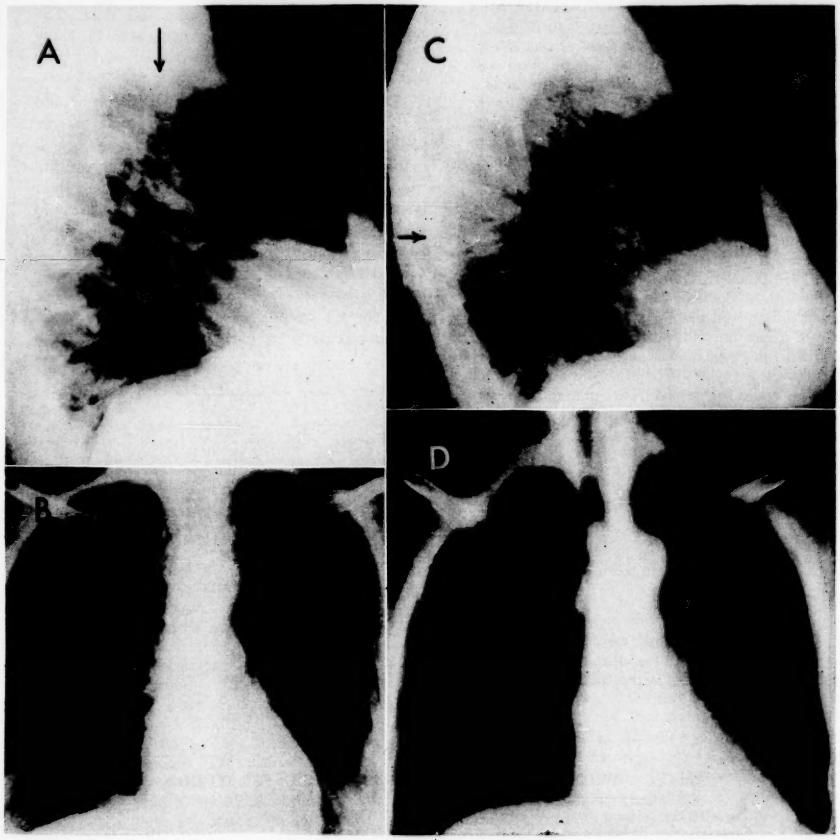
A 48-year-old woman was admitted to the Beth-El Hospital on Jan. 17, 1959, because of respiratory difficulty. She had been well until 1947, when she suffered an attack of bronchopneumonia. Since then she had developed wheezing respiration and had had two or three severe lung infections each year. Her sputum consisted of a scant white or grayish mucoid material, except for insignificant blood-streaking whenever her cough was severe. These minimal hemoptyses had antedated her attack of pneumonia by six years, and the most recent attack had occurred three days prior to admission.

In 1950, because of peripheral blood eosinophilia (8%) and a sputum specimen containing many eosinophils, the patient was referred to one of us (A. I. K.) for therapy. She was found to be very sensitive to any strong odor, and she had positive results for skin tests to house dust and a number of foods. An antiallergen regimen was prescribed—that is, house-dust and autogenous vaccine (sputum) injections, dust precautions, and elimination of positively reacting foods. She was given antibiotics as needed to combat her pulmonary infections.

Nevertheless, at various times during her office visits, it was noted that her wheezing persisted and tended to be more inspiratory than expiratory.

Associate Attending Allergist (Dr. Kleinman) and Associate-in-Charge, Thoracic Service (Dr. Levine), Beth-El Hospital.

Roentgenograms of the chest were taken repeatedly and all were interpreted as within normal limits, with a single exception. A lateral chest roentgenogram taken in 1950 suggested the possibility of a tracheal lesion, emphysema, and osteoarthritis of copist found a profuse amount of thick mucoid material. Aspiration of this resulted in considerable temporary relief. Subsequently, her asthmatoid breathing became worse and finally led to her most recent hospitalization.



A, lateral roentgenogram of chest, taken May 9, 1950. Arrow indicates possible intratracheal density. *B*, posteroanterior roentgenogram of chest, taken Jan. 19, 1959. No lesion is discernible. *C*, lateral roentgenogram of chest, taken Jan. 23, 1959. Possible intratracheal lesion is again seen. Compression of vertebral body is indicated by arrow. *D*, tomogram of chest at 9-cm. level, Jan. 23, 1959. Intratracheal tumor is demonstrated.

the thoracic region of the spine (see figure, *A*). Bronchoscopy was done immediately, and negative results were reported.

She continued to wheeze, and her chest circumference, as measured by her brassiere, increased 4 in. in size between 1950 and 1959. In September, 1958, her inspiratory stridor was so severe that bronchoscopy was again performed. The bronchos-

Physical examination on admission showed an apprehensive woman whose respirations were rapid and so noisy they could be heard from the doorway of her room. She was not orthopneic. With each inspiration a deep suprasternal retraction took place. Her expiration time was not prolonged. Bilateral wheezing and rhonchi could be heard throughout respiration anteriorly and posteriorly.

Her chest was barrel-shaped, with a tendency to kyphosis. Otherwise the physical examination and laboratory tests showed negative results, except for a white blood cell count of 12,000 per cubic millimeter and an increased sedimentation rate of 36 mm. per hour (Wintrobe). Her posteroanterior chest film showed negative findings (see figure, *B*).

Clinically she had the classic signs of an obstruction above the tracheal carina. Lateral films and tomograms were then taken, and the diagnosis of a tracheal adenoma became obvious (see figure, *C* and *D*). There was again seen the abnormality of the thoracic vertebrae, but there was no uniformity of opinion as to whether this represented metastatic disease. A rounded density at the base of the right lung was also present.

Removal of the tracheal lesion was considered urgent, and on Jan. 28, 1959, an operation was performed by Dr. Charles Ripstein, director of surgery, Beth-El Hospital. The sternum was split in the midline, the trachea opened, and 4 cm. above the carina a smoothly covered mass (1 by 1 by 1.8 cm.) arising from a narrow stalk on the right posterolateral wall was removed uneventfully. Her respiratory difficulty cleared immediately and no further wheezing could be heard. The patient was discharged on Feb. 8. The histopathological report was "infiltrating adenoma of the trachea which histologically is a mucoepidermoid variant of cylindroma with many atypical cells."

The patient has continued to be free of pulmonary complaints to the time of her most recent examination (Aug. 27, 1959). She was not dyspneic and did not wheeze. She had no complaints referable to her spine. If indolent metastases were present, they were still asymptomatic in nature.

Comment

This is a case of an allergic person whose symptoms of wheezing and dyspnea were not completely typical of asthma in that inspiratory stridor was present, and who in fact had a mechanical obstruction due to a tracheal adenoma. The intermittent symptoms may be explained by variation in the size of the tumor, depending on the degree of infectious or allergic swelling. The diagnosis became obvious when tomography was done. The suspension of the tumor by a narrow stalk probably explains why it was not discovered during two bronchoscopies.

The 18-year history of minimal hemoptysis and the 12-year history of asthmatic breathing fit very well with the recorded difficulty in diagnosing cylindromas. Cylindromas, whether of the parotid,[1] the breast,[2] or the trachea,[3] are notorious for their late diagnosis. Their metastases are also late and slow growing. The rarity [4] of this low-grade malignancy need not excuse the delay in diagnosis. Use of all available facilities of study can minimize the handicap of rarity. We present this report as a plea for early tomography in any puzzling case of inspiratory stridor or atypical asthma.

232 Lincoln Pl. (17) (Dr. Kleinman).

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CARBON DIOXIDE VERSUS OXYGEN FOR DIAGNOSTIC STUDIES.—Occasional reports of gas embolism with fatal results following the use of air or oxygen in diagnostic Rubin tests led to . . . the use of the more soluble gas, carbon dioxide, as the insufflating agent. Nevertheless, in spite of the widespread acceptance of the hazards involved, air and oxygen continue to be used commonly for tubal insufflation as well as for diagnostic air contrast studies in the practice of urology and surgery. . . . The median lethal doses of intravenous air and carbon dioxide were determined in 89 mongrel dogs. This study showed that air is approximately five times as toxic as carbon dioxide as an intravenous embolic agent. . . . The relative toxicity differential between the two gases in laboratory animals is offered as evidence for the preferential use of carbon dioxide as an insufflating or gas contrast material in clinical practice.—T. D. Graff, M.D., N. R. Arbegast, M.D., O. C. Phillips, M.D., and others, Gas Embolism: A Comparative Study of Air and Carbon Dioxide as Embolic Agents in the Systemic Venous System, *American Journal of Obstetrics and Gynecology*, August, 1959.

GIANT PIGMENTED NEVI

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Giant pigmented nevi afflict the patient not only with an unsightly cosmetic defect but also with the hazard of possible conversion to cancer. Such a nevus, extending over the back of an 18-year-old girl, was removed by surgical excision. Several hundred smaller nevi were removed from other parts of her body surface. Three separate operative procedures were required; the first was to remove the nevi from the right side of her body and prepare a skin donor site, the second to remove part of the large nevus and the smaller ones from her left side, and a third for complete excision of the giant nevus. Almost all the skin grafts were successful, and no malignant changes were found in any of the nevi excised.

Giant pigmented nevi fortunately are uncommon. There have been about 53 cases reported in the literature. The nevus unius lateris as reported by Pack and Sunderland [1] is believed to represent a different clinical and pathological entity. To the 53 cases enumerated we would like to add another which was treated surgically. To our knowledge this nevus represents the largest which has been completely and successfully resected.

Report of a Case

The patient, an 18-year-old girl, first presented herself at Charity Hospital on Sept. 15, 1953, with a giant pigmented nevus which covered her entire back and myriads of small nevi over the remaining body surface (fig. 1). Her principal complaint was that the large lesion emitted a foul odor (due to intermittent ulceration and infection). She also complained of pain and pruritus. The nevus was infected at the time of admission and had been for about three to four weeks. The infection was resistant to local hygienic measures but had healed on a previous occasion after prolonged care.

She was the third of four children in a family in which all were living and well. The mother and one of the siblings have scattered small nevi over their bodies, but no familial or hereditary trait for the giant nevus was evident.

Her birth was a normal spontaneous delivery. The mother gave no history of any unusual prenatal experiences or diseases. The nevus was present at the time of birth and covered her entire back. She was hospitalized for 20 days after birth, during which time the mother stated that radiation therapy was attempted to control the lesion. No appreciable change occurred after this treatment.

The nevus grew and increased in size relative to the normal growth and development of her body. When the patient was 8 years of age a few of the smaller nevi were removed surgically, but the larger lesion was undisturbed. Her last evaluation by a physician was at 13 years of age when numerous small nevi were destroyed by electrocautery. At this time she was again advised against surgery for the large nevus. When she reached the age of puberty, there was no noticeable change in the lesion, although she became more conscious of its presence and infection became a troublesome factor.

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Psychologically she was well adjusted to her cosmetic handicap, although she still found it necessary to keep the lesion constantly concealed. She and her mother both were resigned to the fact that this grotesque disfigurement was irremediable.

Physical examination revealed that she was well developed, well nourished, and of average weight and height. Her back was covered almost entirely by one enormous pigmented hairy nevus which extended from the level of the seventh cervical vertebra, inferiorly, to the level of the lumbosacral junction, a distance of 42 cm. Laterally it extended from one posterior axillary line to the opposite, a distance of 40 cm. The lesion was sharply demarcated from the surrounding normal tissue, not only because of its brownish-black color but also by its elevation, which varied in different areas from 1 to 3 cm. This thickness of the lesion imparted to it a soft and elastic consistency similar to a plexiform neurofibroma. The verrucous surface was marked by numerous papillary excrescences and deep fissures and was covered by an abundant growth of black hair. Exfoliation of friable pieces of the tumor occurred constantly. Over the left scapular region there was an area of ulceration and infection covered by a fibropurulent exudate. No palpable lymph nodes were present in the axilla or elsewhere.

Several hundred small satellite nevi covered her entire body surface (fig. 1). They varied in size, configuration, and color. Some were warty and covered with hair (the nevus pilosus verrucosus);

others, such as those found on the palms of the hands and soles of the feet, were flat (nevus spillus). A number of circular scars containing pigment were dispersed over both legs and thighs. These represented sites of inadequate cauterization with residual nevus cells scattered in the scar tissue.

Fig. 1.—Patient aged 18 showing gigantic nevus and multiple satellite nevi over entire body.

The patient was prepared for surgery Sept. 28, 1953. The first procedure consisted of excision of multiple small nevi over the right side of the body. This included the palm of the hand, the sole of the foot, the entire thigh, the leg, where incomplete cauterization had been performed, and the right side of the abdomen. The rationale for proceeding in this manner was to remove all the precancerous lesions first, while at the same time preparing a donor site. It was also undesirable to completely incapacitate the patient by operating on both hands and feet simultaneously. In this way she could be ambulatory two or three days after surgery. A general anesthesia was administered, and with two surgical teams at work about 200 nevi were elliptically excised and closed primarily. On Oct. 10, 1953, a similar procedure was performed on the opposite side.

After a short leave from the hospital she was readmitted for a third operation which was performed Nov. 10, 1953. Under endotracheal anesthesia three large strips of skin of about 17/1,000 in. in thickness, 40 cm. in length, and 8 cm. in width were removed with a vacuotome from the left thigh. Her position was changed, and about one-third of the lesion was excised and grafted. An estimated 95% take of the grafts was noted. She was discharged from the hospital two weeks after surgery.

Her final surgical procedure took place Jan. 12, 1954, at which time the remainder of the lesion was excised. Four strips of split-thickness skin, taken from the right thigh, were used to reconstruct the area. One hundred per cent acceptance of the grafts occurred. Healing was rapid, and was followed by a course of physical therapy and oil massage.

Fig. 2.—Photograph taken May, 1954, five months after final procedure, showing complete healing.

The patient was photographed when last seen in May, 1954 (fig. 2). The area was covered by soft, pliable, freely movable skin with only slightly ab-

normal sensation. She was more than well satisfied with the results, and her mental outlook had markedly improved.

Histopathology.—Representative sections were taken from various portions of the giant nevus for microscopic study. In general, the histological picture conformed throughout with few exceptions. Study of the epidermal layer revealed an irregular, verrucous surface covered by an atrophic, hyperkeratotic, stratified squamous epithelium. The continuity of the epidermis-cutis junction was uninterrupted in most sections, but increased cellular activity was noted in one specific area in the stratum spinosum. Here spherical aggregations of melanoblasts surrounded by a residual wall of epidermal cells were poised at the epidermis-cutis junction in apparent readiness to detach themselves and enter the underlying stroma (fig. 3). This was the only evidence of junctional activity seen in the sections. Immediately beneath the epidermis, nevus cells were seen in varying arrangements. More superficially they were grouped as elongated cords or oval clusters (fig. 4). They also were found in

Fig. 3.—Photomicrograph under high-power magnification showing junctional activity. Note aggregations of melanoblasts with central group breaking into dermis.

solid sheets or scattered individually throughout the stroma. In the deeper layers of the dermis and subcutaneous tissues was found a gradual transition of the nevus cell from the more polygonal cell of the papillary layer to a cell resembling a fibroblast or Schwann cell (fig. 5).

The diagnosis was giant compound neuronevus and multiple neuronevi, predominantly intradermal, with some junctional components.

Management

Generally speaking, all giant pigmented nevi should be surgically removed; not only to overcome

Fig. 4.—Low-power magnification illustrating arrangement of nevus cells into cords and clusters in superficial dermis.

the cosmetic blemish but to avoid the possible future hazard of degeneration or malignant transformation. There will be but few cases that fall into the categorically inoperable class because of their extensiveness.

In our opinion, there is but one safe and satisfactory means of removing these lesions, and that is complete surgical excision with use of the scalpel. Electrocautery, electrodesiccation, and radiation have been used in their treatment, but this is to be condemned. These agents all too frequently inadequately destroy the lesion, and thereby cause irritation which might be the stimulus to malignant transformation.

If possible, these lesions should be removed in childhood when the sensibilities of the patient have not been affected by his contact with the outside world. Performance of surgery at this age, as in McDowell's [2] case, results in better healing, lessened cosmetic disfigurement, and prevents degeneration and possibly malignant transformation of these tumors.

The question of removal of the lesion *in toto* or in stages will depend largely on the individual patient. Pack and Livingston [2A] express the belief that after puberty multiple-stage procedures should not be performed because of danger of malignant transformation. We agree with this theoretical premise, but feel that good surgical judgment will necessitate the removal of some of these lesions in stages.

Comment

Physical anomalies occasionally provide undesirable psychological reactions. The average person may have from 18 to 100 nevi, none of which causes

Fig. 5.—Low-power magnification of deeper portion of dermis and subcutaneous tissue. Note similarity to structure of neurofibroma.

undue apprehension, some of which may even be referred to as beauty marks; however, the giant nevus represents a stigma which causes its host to feel self-conscious and socially unacceptable, creating a profound distortion of his personality. It is appalling how frequent lesions which are remediable will be allowed to persist and progress to the point where they affect the person's mental equilibrium.

Aside from its esthetic detraction and psychological sequelae, the malignant potentiality should be considered. Although it has been stated by some authorities that giant nevi never become malignant, evidence at hand seems to disprove this. Of the 53 cases which have been recorded in the literature 7 [3] are known to have developed into a malignancy. This is a 13% incidence. Infection and chronic irritation appear to be the most common stimulus. When the question of malignancy in giant nevi arises, one must search its histogenesis for the answer. No matter which theory of origin of pigmented nevi one holds, the nervous or epithelial, it is a well-established fact that cellular nevi with junctional characteristics are more susceptible to neoplastic change. It has generally been assumed that most giant nevi are of the intradermal type, and are therefore unlikely to become malignant. Although this may be true in part, by virtue of the fact that the predominant histological characteristics of the lesions are intradermal, nevertheless, the existence of but one small zone of junctional activity is sufficient evidence for the diagnosis of a compound nevus. This case illustrates how easily one might have overlooked the single, small area of junctional activity (fig. 3) and arrived at an erroneous diagnosis of intradermal nevus. It is probable that in many cases of giant nevi areas of junctional activity go unrecognized because few sections are cut.

Another possible explanation for the misconception that all these lesions are solely intradermal is failure to realize that progressive changes occur in the histology of the nevus throughout its life. This was pointed out by Lund and Stobbe.[4] Proliferation at the junctional zone may occur either early or late in their natural history. When this change appears the nevus can no longer be classified as intradermal but must be considered a compound nevus, with its precancerous implication. We therefore conclude that all giant nevi are potentially malignant and should be removed when the patient is at an early age.

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CLINICAL NOTES

ADDUCTOR MUSCLE INJURIES IN BOWLERS

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Bowling is considered a sport of little hazard and, as such, has not rated mention in recent articles on athletic injuries. Bowling injuries have usually been limited to fingers pinched in the ball rack and occasional toes bruised by dropped bowling balls. The cases here discussed concern another injury which can be related to the peculiar mechanics of bowling. The problem involves strain, and in one case actual avulsion, of the muscles of adduction of the thigh. Stress on these structures occurs during braking at the foul line on delivery of a bowling ball.

Report of Cases

CASE 1.—A man, aged 44, weighing 220 lb. (99.9 kg.), 6 ft. (183 cm.) tall, with a heavy, protruding abdomen, sustained an injury to the right groin while bowling on Nov. 25, 1958. I observed the accident throughout its course, since I am a member of the patient's bowling team.

The patient, because of his formidable size, habitually delivered his ball while in a more erect position than the average bowler. On this occasion he threw the ball in an unusually powerful fashion, obtaining a resounding strike. He stopped firmly at the foul line in his erect position. In obvious severe pain, he then staggered and grasped the bowling ball rack in an effort to keep from falling. He paled and sweated profusely. He was placed in a reclining position, and in a few minutes the appearance of shock abated. Examination revealed an enlargement in the right inguinal region extending into the upper portion of the right side of the scrotum. The mass did not have the usual appearance of a hernia, since it lay somewhat posteriorly in the perineal region in addition to its extension into the scrotum. The mass was tender and not discolored, and the enlargement was not reducible by taxis. No previous swelling had been noted in this region by the patient. The initial diagnosis was probable incarcerated, acute, right inguinal hernia, with the posterior development of part of the mass noted as one unusual feature.

The patient was transported by ambulance to St. Nicholas Hospital, with no further attempts to stand or walk. He continued to have pain in the right groin and the medial aspect of the right thigh. On admission his blood pressure was 128/80 mm. Hg, pulse 88 per minute. The patient, having eaten a large supper, had his stomach evacuated by means of a Levin tube and suction. The pain remained marked. After consultation with his family physician (who was also bowling in the same league), the patient was admitted to surgery three hours after his injury.

Operation.—With the patient under general anesthesia, with intratracheal intubation and gastric suction, a right inguinal incision was made over the irreducible mass. The adipose panniculus was about 3 in. (7.6 cm.) in thickness. On exposure of the external oblique muscle dark, reddish-blue discoloration, apparently hematoma, was noted through the aponeurosis. This aponeurosis was divided, exposing the cord, which contained a large quantity of extravasated blood throughout its length. There was also a great amount of clotted blood in the inguinal canal and scrotum. No evidence of severe, active bleeding was present, however. Examination of the inguinal region revealed no sign of relaxation of the internal ring nor any hernial sac. The spermatic cord and testis were delivered into the wound. There were many large areas of hematoma throughout these structures.

Further exploration revealed a tear in the terminal floor of the inguinal canal at its entry into the scrotum. At this site disruption of the right adductor tendon (apparently mostly the adductor longus) at its origin from the front of the pubis was demonstrated. A splinter had been torn from the pubic bone along with this tendinous structure. From the relations demonstrable it appeared that the tearing of this bony structure across the posterior aspect of the cord had lacerated the vessels to the right testis, causing the bleeding into these tissues.

The degree of disruption of the blood supply to the testis and the amount of visible hematoma in the cord and testis made their removal mandatory. This was accomplished. Repair of the adductor tendon, reconstructing its insertion onto the pubic bone and further reinforcing the attachment by means of sutures to the adjacent adductor tendon group, was made. No further bleeding was noted. The defect in the floor of the inguinal canal and the operative opening in the external oblique muscle were then closed, and the subcutaneous tissue and skin were reunited without drainage.

Surgeon, the Sheboygan Clinic.
Read before the Wisconsin Surgical Society, Oshkosh, Wis., Sept. 19, 1959.

The postoperative course of the patient was without disturbing incident. Early ambulation on crutches was possible, the patient being adjured against adducting and abducting his right leg. He was discharged from the hospital on crutches on the 12th postoperative day. On Dec. 17, 1958, evidence of hematoma of the inguinal region and scrotum had practically disappeared. Testing of adductors at this time demonstrated their integrity. The crutches were discarded on Dec. 24, 1958.

On Jan. 7, 1959, the patient walked well, with no demonstrable weakness of the right adductors. On Feb. 21, 1959, he engaged in his first postoperative bowling, with a score of 463 in a three-game series, including one game with a score of 192. This, he claims, compared satisfactorily with his preinjury state. On Feb. 25, 1959, at examination he had no discomfort and no apparent disability on walking, climbing and descending stairs, and engaging in his usual activities.

Case 2.—A man aged 45, a physician, 6 ft. 3 in. (190.6 cm.) tall, weighing 200 lb. (90.8 kg.), during the same bowling season sustained an obvious adductor strain. The patient experienced his injury by slipping, while attempting to deliver his bowling ball, when his left foot caught on a wet spot on the alley. This brought him violently to a halt. The patient described his distress as a sudden, whip-like pain from the leg throughout the body to his head, but concentrated in the left groin. Examination revealed no swelling or apparent disruption of structures but acute tenderness of the adductor gracilis region of the upper medial part of the thigh. The initial severe pain passed quickly, but discomfort in the left groin was of sufficient degree to prevent the patient from bowling for a period of about two weeks. Subsequently, he noted some dropping in his bowling score, as compared to preinjury levels, because of caution induced by his strain. The discomfort in the left groin persisted for four weeks.

Case 3.—A man aged 56, a dentist, of medium build, also experienced pain in the left groin on making a sudden balk at the foul line. His uncomfortable injury occurred in January, 1959. While examination revealed only tenderness in the region of the origin of the adductors and slight tenderness in the upper medial thigh, the patient's discomfort was of such degree that he avoided bowling for most of the remaining bowling season. No hematomas developed. By April, 1959, his discomfort had abated.

Case 4.—A man, aged 45, a city sanitation department employee, developed pain in the right upper medial thigh region on July 7, 1959, on lifting a large, heavy garbage can, overly filled, to his knee and then into the receiving port of his sanitation truck. The patient is slender but muscular. On the occasion of lifting the ungainly object he was forced to strain excessively to control it. He was examined a few hours after the incident. There was demonstrated no inguinal or femoral hernial impulse. The scrotum and contents appeared normal. The patient had almost exquisite tenderness over the upper course of the right adductor muscles, particularly the gracilis, became faint after gentle palpation of these muscles, and was forced to lie down for 10 minutes. No ecchymosis was evident. The diagnosis was strain of the right adductor femoris muscles. Treatment consisted of diathermy for two days and administration of analgesics. On July 10, 1959, there still remained moderate tenderness over the adductor region, but not of the exquisite nature earlier noted. There was a slight amount of induration apparent on palpation of the adductors on this day. He returned to work July 13, but because of pain in the upper medial thigh region he again ceased to work. Further diathermy treatment was then administered.

On July 21, 1959, he walked without a limp, although he still had slight tenderness on compression over the right adductor longus muscle. The discomfort had reduced sufficiently to permit the patient to return to work on July 22, 1959.

Comment

The case reports illustrate varying degrees of injury to the adductors of the thigh. Three concern injury incurred on suddenly stopping in a somewhat awkward position. The fourth occurred during an unexpectedly difficult lifting motion while hoisting a well-loaded garbage container onto a truck. They all involve strain, and in one case disruption, of the adductors, in each case of one thigh.

Strains are considered tearing of strands or fibers within a muscle, without complete division of the muscle itself. The injury may or may not be accompanied by external evidence of ecchymosis. The most severely injured patient (case 1) sustained disruption of the adductor longus at its origin and further injury, by laceration with a bone fragment, to the spermatic cord.

Adduction of the thigh is produced by several muscles, including the lower fibers of the gluteus maximus, but primary adduction is the function of the three adductor muscles, longus, magnus, and brevis, and the pectineus. In addition, the gracilis functions both as an internal rotator and an adductor. When the lower extremity is fixed, these muscles, taking their fixed points from the leg, act on the pelvis to help maintain the body in an erect position and, as in the cases here outlined, to prevent forward displacement of the body on an extended leg.

Another example of adductor action is grasping the sides of a saddle between the knees during riding. Christopher [1] mentioned a strain of the thighs, which he described simply as "rider's thigh." He may have thus been referring to another form of adductor strain.

Instances of complete disruption of a muscle or tendon are fairly common. Examples include (at the shoulder) ruptures of the supraspinatus and infraspinatus, the subscapularis tendon, and the long tendon of the biceps brachiae. Mathé [2] described an instance of traumatic avulsion of the psoas muscle which, by fibrosis, produced attacks of renal colic after three years. Disruption of the adductor longus muscle requires, as in these other disruptions, unusual force generally applied in an unnatural manner.

Prevention.—The importance of sound physical conditioning in the prevention of athletic injuries has frequently been emphasized. These injuries add emphasis to this basic principle. Case 2 resulted from an unexpected checking of motion at a wet spot on the alley. Cases 1 and 3 resulted from violent stopping efforts in an overly erect position at the foul line. These can be avoided by an altered approach to the foul line and by "following through" rather than braking violently. Case 4 involved the lifting of an unexpectedly heavy, large container, in an awkward manner, to the thigh and into a truck bed. The prevention of this, an industrial injury, concerns the use of proper lifting methods and of adequate assistance in lifting heavy objects.

Treatment.—Disruption of major tendon structures requires early, meticulous reconstruction and prolonged convalescent disuse. This was accomplished in case 1 by use of crutches and avoidance of adduction, abduction, and weight-bearing on the involved leg. Strains present a different treatment problem. Here early mobilization (avoiding excessive strain) is essential to avoid limiting fibroses and prolonged disability. Administration of analgesics and adjunctive physical therapy are helpful in achieving this early mobilization.

Conclusions

Four cases of injury to the adductor muscles of the thigh occurred; three in bowlers and the fourth in a public employee as a result of an industrial lifting accident. With disruption of the adductor longus, one of the bowlers required major surgical treatment. Prevention of such injuries entails proper conditioning and training.

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RENAL ARTERY ANEURYSM PRODUCING RENAL INFARCTION WITH RESULTANT HYPERTENSION

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A comprehensive review of the literature on true aneurysms of the renal artery reveals prior reporting of 142 cases. It is a rare pathological entity which occurs with a frequency of less than 0.015% [1]; in the case of renal infarction it has been reported as 1.4%.[2] The true incidence of hypertensive vascular disease in man is unknown, but the record of living subjects suggests that it is 24% or greater in the population ranging from the third to the seventh decade of life.[3]

A case report follows, in which an aneurysm of the renal artery was believed to have been responsible for infarction leading to renal hypertension. The hypertension was subsequently relieved by a nephrectomy.

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Report of a Case

A 47-year-old man was seen as an outpatient on Dec. 30, 1955, complaining of severe right costovertebral angle pain, with radiation into the flank, of several days' duration. The patient also complained of severe headaches. Microscopic hematuria was found on several occasions.

The patient's history revealed that he had had a thrombosis of the veins of his left leg one year prior to the examination and had made an uneventful recovery. There was no other evidence of vascular disturbance and no familial history of renal disease.

Examination revealed the following significant findings. Blood pressure was 200/120 in the right and 210/120 mm. Hg in the left arm. Examination of the abdomen revealed tenderness to jarring percussion over the right costovertebral angle. Rectal

examination was noncontributory. Intravenous urograms were done and found to represent normal findings bilaterally. Complete urinalysis revealed an albumin content of 3+ and an occasional red blood cell. The urine was centrifuged and many granular casts, both coarse and fine, were observed. Prior to this time there had been no knowledge that hypertension existed. The patient did not return for further evaluation but entered a veterans' hospital a few weeks later; during his hospital stay he experienced a recurrence of his right flank and right costovertebral angle pain, which persisted over a period of several days. After a few weeks he was discharged on a medical regimen for hypertension. His blood pressure remained elevated, however, and subsequently he was again observed and the possibility of renal infarction was considered.

The patient was admitted to the Orange Memorial Hospital in May, 1956, and the following day a lumbar aortogram was carried out which showed a decreased blood supply of the lower pole of the right kidney. The blood pressure readings while he was in hospital ranged from 192 to 150 mm. Hg systolic and 120 to 100 mm. Hg diastolic. A few days later, a right nephrectomy was carried out, with a preoperative diagnosis of right renal infarction. The renal artery was palpated and found to be markedly dilated, approximately 2 cm. in its greatest diameter just before its bifurcation. After further dissection it was realized that an aneurysm was present, and giving rise to the enlargement of the renal artery. Chromic ligatures were placed proximally to the aneurysm, and the kidney was removed without further difficulty. The preoperative blood pressure of 200/100 immediately dropped to 140/80 mm. Hg and remained such throughout the remainder of the procedure. The pathological report showed a kidney which weighed 150 Gm. There was 2 cm. of renal artery which, at the point of resection, showed an open sacular dilatation, about 1.5 cm. in diameter, which was partially lined by clots. No occlusion was noted in the renal artery or vein. There was a large depressed, sharply delineated scar occupying the posterior aspect of the kidney, measuring 6 by 5 cm. and extending across the midline to involve a small portion of the opposite half. This part of the kidney was a very dark red, and sections showed the dark red color to extend to a depth of about 0.7 cm.

Microscopic examination revealed extensive tubular atrophy in the scarred area, with resultant contraction of the glomeruli. In the medulla the tubules were moderately dilated and filled with hyaline casts. The pathological diagnosis was one of a large healing infarct of the right kidney and a sacular aneurysm of the right renal artery.

The patient was discharged on the eighth postoperative day and came for follow-up examinations in the office at six-month intervals, during which period his blood pressure remained normal. He was last seen in the office two and one-half years later, when his blood pressure was 122/90 mm. Hg. The patient has been rehabilitated in that his headaches have disappeared, his blood pressure has remained normotensive, and he has resumed his usual occupation since surgery.

Comment

The most frequent signs and symptoms of renal aneurysm are pain in 50% of patients, hematuria in 35%, palpable mass in 25%, hypertension in 15%, and bruit in 10%. Calcification in the wall of the aneurysm was found in only 25% of reported cases.[4] Sudden, persistent flank pain, associated with varying degrees of generalized collapse or shock, nausea and vomiting, and distention of the intestinal tract constitute the symptom complex of renal infarction.[2] The urine is often grossly bloody, although it may be clear initially. An adequate history helps to determine whether the infarction is arterial, venous, or traumatic. Diagnosis of a complete renal infarction is almost certain when excretory urograms show marked decrease or absence of function in the affected kidney and retrograde pyelograms reveal a normal collecting system and pelvis, without ureteral obstruction. Diagnosis in partial infarction, however, is difficult to make with intravenous urograms, as the reserve function in the unaffected portion of the kidney may fill the collecting system with sufficient contrast material to give a normal-appearing urogram.

In anyone with sudden onset of hypertension preceded by flank pain one should consider thrombosis or embolism of the renal artery. In any constriction of the renal artery the involved kidney will be smaller and softer. Unless contraindicated, all hypertensive patients should have intravenous urograms. The renal mass, even though reduced in size, may not always be demonstrable. The patient will also have a decrease in renal function, which may or may not be detectable.

In diagnosing renal hypertension cystoscopy and bilateral ureteral catheterization, with differential renal function studies, will be helpful. Another diagnostic aid is measurement of the urine volume and sodium concentration from each kidney. In ischemic kidneys, the urine volume and the sodium concentration are decreased; this was initially demonstrated in dogs by White [4A] a few years ago. Recently, Winter [5] used radioactive iodopyracet (Diodrast) compound in renograms, which method may provide a screening test of practical value. Renograms have also been performed by means of a radioactive tri-iodinated medium (Renografin).[6] Previously, aortography had been used to confirm the diagnosis in questionable cases; at present, however, we are more reluctant to use this procedure because of reported adverse reactions.

Hypertension can be divided into two categories based on etiology,[1] which are (1) essential hypertension which has no known cause and (2) secondary hypertension which has a recognizable cause.

The diagnosis of essential hypertension is usually made by exclusion. Any sudden onset of severe hypertension should be considered of the secondary type until complete study reveals no known cause. Renal hypertension is the result of renal arterial lesions or due to parenchymal disease.

Histologically, one may predict the prognosis for hypertension in these unilaterally nephrectomized patients. A more satisfactory result is usually obtained in those patients whose kidneys pathologically reveal tubular atrophy, which is secondary to diminished blood flow. In those patients whose kidneys do not reveal the ischemic type of tubular atrophy, however, no benefit is obtained from the nephrectomy as far as relief from hypertension is concerned.[7]

Smith [3] has presented the case of unilateral renal disease in the hypertensive state very comprehensively. His study indicates that benign or accelerated hypertensive disease can be the result of unilateral renal disease and that it may be amenable to surgical correction. The incidence of successful nephrectomy for hypertensive disease has been estimated at 26%. However, if satisfactory results are to be obtained, the wise selection of cases amenable to surgical correction is important. The criteria considered necessary for a judicious selection [3] are (1) hypertension of less than two years' duration, (2) a persistent downhill course, (3) headaches and retinopathy (minimal changes), and (4) a diastolic blood pressure of 120 mm. Hg or more. Persistent lowering of blood pressure to 140/90 mm. Hg or lower for one year and alleviation of symptoms should be observed before a particular case is reported as cured.

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Summary

In a case of true aneurysm of the renal artery, with subsequent infarction and hypertension, the latter condition was successfully relieved by nephrectomy. Although in this instance diagnosis was established by means of a lumbar aortogram, the performance of a renogram may provide a useful screening test, without the potentially adverse reactions recently ascribed to aortograms. If four major criteria are observed for a wise selection of cases, nephrectomy for hypertensive disease can be a successful procedure.

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HEALTH CARE COSTS.—Abandonment of our system of private medicine and voluntary insurance for any government scheme could well be the straw that breaks the back of the American economy. Social Security benefits already promised, even if not further expanded in accordance with congressional election year custom, will require, by 1969, the collection of $216 per year from every worker earning $4800 per annum and a like sum from his employer. Today, for many, Social Security taxes exceed their income taxes. It is naive to assume that there is no limit to what government can exact from the citizen. Government creates no wealth. It can only take from one person and give to another while losing considerable of the nation's economic life-blood in the transfusion. Yet fully one-quarter of the 7300 bills now pending in Congress would confer special benefits on certain segments of the population without adequate provision for payment of these benefits. Enormous government spending even without the intensifying factor of recurrent deficits is the carcinogenic agent that triggers the cancer of inflation by increasing the cost of doing business at all levels while dampening economic incentives.—E. J. Faulkner, Chairman-Elect of the Health Insurance Council, Common Sense and Health Care Costs, *The Nebraska State Medical Journal*, August, 1959.

SPECIAL ARTICLE

PRESENT STATUS OF TREATMENT OF PERNICIOUS ANEMIA

NINTH ANNOUNCEMENT OF U. S. P. ANTI-ANEMIA PREPARATIONS ADVISORY BOARD

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The report in 1926 by Minot and Murphy [1] of the effectiveness of liver therapy in pernicious anemia soon was followed by the development of active concentrates of liver suitable for clinical use. By 1936 relatively purified extracts of liver were available for intramuscular injection, in addition to those preparations which earlier had been developed for oral administration. Owing to differences in animal sources and in manufacturing methods, the therapeutic effectiveness of these substances was not directly related to the amount of liver from which they were derived and could be estimated only by clinical tests of the final product.

Standardized Liver Concentrates

Standardization of preparations intended for the treatment of pernicious anemia was first prescribed by the *Eleventh Decennial Revision of the Pharmacopoeia of the United States* on June 1, 1936, as the responsibility of the Anti-Anemia Preparations Advisory Board.[2] In 1938, the Board defined as a U. S. P. unit that amount of a preparation which, when administered daily to patients with pernicious anemia, produced a satisfactory hematopoietic response. Since much more of a given liver preparation was required to produce therapeutic effects when administered by the oral route than when injected intramuscularly, the unit was further designated as either "oral" or "injectable," depending on the mode of administration. The Board was charged with the responsibility of reviewing and assessing confidential data submitted by pharmaceutical manufacturers pertaining to source of material, method of preparation and handling, packaging and labeling, and therapeutic effects of preparations intended for treatment of pernicious anemia. The assignment of units was based on the results of clinical assays employing three or more patients with pernicious anemia in relapse whose erythrocyte and reticulocyte responses were expected to approximate values obtained in previous experience with preparations known to be potent.[3]

†Dr. Bethell, Chairman of the U. S. P. Anti-Anemia Preparations Advisory Board, died April 22, 1959.

Vitamin B_{12} in Liver Extracts

It was not until the isolation of vitamin B_{12} in 1948 that the identity of the anti-pernicious anemia principle of liver was established. Thereupon clinical trials soon provided convincing evidence that vitamin B_{12} is the principal, if not the sole, anti-pernicious anemia factor of purified liver extracts. When quantitative methods for measurement of the concentration of vitamin B_{12} became available, a study was conducted under the auspices of the U. S. P. to determine the vitamin B_{12} content of various preparations of liver for parenteral use to which U. S. P. units had been assigned. The results of this study showed that there was a considerable range of concentrations of vitamin B_{12} in preparations to which the same U. S. P. unitage had been assigned.[4] this was not a surprising finding, in view of the fact that clinical testing of consecutive lots manufactured by the same process was rarely possible, and because the variable responses obtained in different patients receiving the same preparation already had indicated the relatively crude nature of such clinical assays. Accordingly, in 1952, use of the U. S. P. unit (injectable) was discontinued, and the measure of activity of preparations intended for parenteral use became the vitamin B_{12} content of the preparations, as determined by official microbiological assay.[5]

More than a decade of experience now has amply confirmed the belief that parenterally administered vitamin B_{12} is as effective as injection of purified liver extract of equivalent vitamin B_{12} content, in the treatment of pernicious anemia. Patients who receive injections of appropriate amounts of vitamin B_{12} in either form at regular intervals remain in hematological remission and do not develop neurological or gastrointestinal manifestations of the disease. Vitamin B_{12} (cyanocobalamin, U. S. P.), a pure crystalline substance, is available in much higher concentration than in liver extracts, is nonirritating and nontoxic when injected, and is less expensive than in the form of liver preparations. For initial treatment of the patient in relapse, the dosage schedule employed is not a matter of great impor-

tance, since rapid clinical and hematological improvement appear to follow the injection of a single dose of about 30 mcg. Nevertheless, in order-to restore the vitamin B_{12} concentration of depleted tissues, it seems wise to repeat the injection daily or several times a week, at least during the first week of therapy. An injection of as little as 30 mcg. of vitamin B_{12} given once each month is sufficient to maintain clinical and hematological remission indefinitely. However, it is now recognized that this amount is inadequate to restore the serum concentration of vitamin B_{12} to normal levels; therefore, larger maintenance doses are justified. The treatment of pernicious anemia with vitamin B_{12} given by the parenteral route thus is a sure and convenient therapeutic measure.

On the other hand, the treatment of pernicious anemia with orally administered substances presents a complex problem. That effective therapy can be provided by the oral route was first demonstrated by Minot and Murphy.[1] However, it has long been known that much more is required of a given liver preparation when administered orally than when injected. Thus, hematological responses comparable to those following the daily injection of a U. S. P. unit of liver extract are usually produced by the daily injection of 1 mcg. of vitamin B_{12}. Some patients have had satisfactory responses to the oral administration of 25 mcg. of vitamin B_{12} per day; others have failed to respond to amounts as large as 250 mcg. per day. The reason for this now seems clear. Vitamin B_{12} is a large molecule which does not easily cross the intestinal mucosa. Normal persons appear to absorb little more of the vitamin from the usual mixed diet than the minute amount which is physiologically required, perhaps less than 1 mcg. per day. Absorption of even this small quantity is made possible by the presence in the normal gastrointestinal tract of "intrinsic factor," a substance produced by the gastric mucosa and apparently having the properties of a mucoprotein.

Intrinsic factor, by a mechanism which, at present, is not clearly understood, facilitates the absorption of vitamin B_{12}. The therapeutic use of the U. S. P. preparations powdered stomach, liver with stomach, or vitamin B_{12} with intrinsic factor concentrate depends, in each instance, on the activity of intrinsic factor in enhancing the absorption of the vitamin B_{12} in the product. However, the therapeutic effectiveness of mixtures of intrinsic factor and vitamin B_{12} cannot be estimated from the vitamin B_{12} content of the preparation. Although intrinsic factor concentrates of considerable potency have been prepared, the active agent has not been obtained as a pure substance and no simple laboratory test of established validity has been available by which its concentration and activity can be measured. Accordingly, to standardize preparations intended for the oral treatment of pernicious anemia, clinical trial is still essential, and it has been necessary to retain the U. S. P. unit (oral). In the assignment of units to such preparations the Board required that the final product of a specified manufacturing procedure, which contained the mixture of vitamin B_{12} and intrinsic factor to be marketed, be given to at least three patients with untreated pernicious anemia. In this way, numerous products containing liver and stomach or vitamin B_{12} and intrinsic factor concentrate have been demonstrated to produce satisfactory hematopoietic responses during clinical assays. Nevertheless, it cannot be inferred from these responses that all other patients with the disease will react as well.

Vitamin B_{12} Injections

Several considerations have led to the fear that oral administration of products to which U. S. P. units have been assigned may not always provide adequate treatment for patients with pernicious anemia. Certainly the amount of vitamin B_{12} that can be absorbed from the gastrointestinal tract, even from preparations containing intrinsic factor, is very small in comparison with the amounts which are readily injected parenterally. Intensive initial therapy cannot be provided with the preparations currently available for oral use. A single injection of 30 mcg. or more of vitamin B_{12} in patients with pernicious anemia in relapse is regularly followed by peak reticulocyte responses within five or six days. In contrast, when orally administered preparations are given at the usual dose of one U. S. P. unit daily, the peak of the reticulocyte response is usually delayed, often to about the 10th day. Moreover, in some patients with pernicious anemia, besides lack of intrinsic factor, defects of intestinal absorption may limit assimilation of vitamin B_{12}, especially when oral therapy is first begun.

Lifelong therapy with vitamin B_{12} is required in pernicious anemia, since the gastric lesion responsible for the deficit of intrinsic factor cannot be repaired. Recently a number of reports have appeared which indicate that some patients with pernicious anemia have experienced relapse while apparently receiving usual doses of vitamin B_{12} with intrinsic factor concentrate.[6] In some instances the patients had displayed initial satisfactory responses to treatment; but then, in spite of continued administration of the same preparation, anemia and other manifestations recurred. There is now good evidence that this is the result of an acquired refractoriness to certain intrinsic factor concentrates derived from animal sources. Tests with tracer doses of radioactive vitamin B_{12} have indicated that the intrinsic factor concentrates in question no longer appreciably enhance the absorption of vitamin B_{12} in these patients, although the same preparations are active in previously untreated patients. Development of such refractoriness has been observed within several months of the onset of oral therapy. In patients who had become unresponsive to such

preparations, normal human gastric juice exerted its usual effect of potentiating absorption of vitamin B_{12}. Furthermore, in some instances other preparations of intrinsic factor from the same or different animal sources were effective. These observations have led to a series of investigations concerning the nature of the refractory state and the conditions under which it occurs. Some preparations seem to lead to the development of refractoriness more frequently than others, and quite possibly some do not have this action at all. At the present time, however, there is no means by which one can be assured that a product will not have this property for some patients. Preparations to which units have been assigned on the basis of the usual clinical assays thus may not be satisfactory for maintenance therapy of some patients with pernicious anemia. In the management of a disease for which parenteral therapy with vitamin B_{12} is a completely adequate and wholly reliable form of therapy, it is unwise to employ a type of treatment which is, at best, unpredictably effective.

Comment

The Sixteenth Revision of the U. S. P., which will become official late in 1960, will not include preparations intended for the treatment of pernicious anemia by oral administration. The U. S. P. unit will cease to exist, and the Anti-Anemia Preparations Advisory Board, having no further function, will be disbanded.

601 N. Broadway (5) (Dr. Conley).

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THE PREVENTION OF SCHIZOPHRENIA.—The gloomy view is sometimes taken, even by experts, that there can be little chance of preventing schizophrenia by public health measures when the hereditary forces seem so strong. This view is fallacious and can be refuted by pointing to the fact that twin-studies on tuberculosis show a genetic factor of precisely the same order as that shown by schizophrenia. To produce any disease, there must be a combination of genetic and environmental factors, and if the latter are sufficiently favorable then the disease will not develop, however strong the genetic loading. Rickets is another illustration of this, as Fraser Roberts has pointed out: 150 years ago it was considered hereditary; and so it is, in the sense that some people are genetically disposed to it and others genetically resistant. Yet once it was learned how to avoid the environmental factor (lack of Vitamin D) the disease became preventable and disappeared.—E. H. Hare, The Epidemiology of Mental Illness, *The Royal Society for the Promotion of Health Journal*, July-August, 1959.

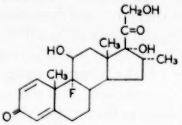
COUNCIL ON DRUGS

NEW AND NONOFFICIAL DRUGS

The following descriptions of drugs are based on available evidence and do not in any case imply endorsement by the council.

H. D. KAUTZ, M.D., *Secretary.*

Dexamethasone (Decadron, Deronil, Gammacorten).—9α-Fluoro-16α-methylprednisolone.—The structural formula of dexamethasone may be represented as follows:



Actions and Uses.—Dexamethasone is a synthetic analogue of hydrocortisone, with similar actions and uses. It is the most potent anti-inflammatory glucocorticoid yet available. Laboratory and clinical experience indicate that doses of 0.75 mg. of dexamethasone produce an anti-inflammatory response equivalent to that of about 4 mg. of triamcinolone or methylprednisolone, 5 mg. of prednisone or prednisolone, 20 mg. of hydrocortisone, and 25 mg. of cortisone. However, this greatly increased potency does not necessarily confer upon dexamethasone any special therapeutic advantage over other steroids with essentially the same pharmacological effects. Thus, except for using much smaller doses, therapy with dexamethasone may be expected to give results essentially the same as those anticipated with triamcinolone, methylprednisolone, prednisone, and prednisolone. As with the latter drugs, dexamethasone appears to lack the sodium-retaining and potassium-excreting properties of the earlier gluco-corticoids, cortisone and hydrocortisone. In fact, it may at first have a diuretic effect when substituted for cortisone or hydrocortisone in patients made edematous by these agents. In this respect, dexamethasone is well suited for long-term therapy in which steroid-induced fluid retention and electrolyte imbalance might otherwise become a problem. By the same token, the lack of mineralocorticoid activity with dexamethasone makes it inferior to cortisone, hydrocortisone, or fludrocortisone for replacement therapy in adrenal cortical insufficiency (Addison's disease). Hence, dexamethasone is used principally for its anti-inflammatory and antiallergic effects. It is useful in appropriate cases of rheumatoid arthritis and other collagen diseases, allergic conditions, inflammatory eye diseases, certain leukemias and lymphomas, soft tissue inflammations, hemolytic anemias, and other conditions generally considered responsive to systemic glucocorticoid therapy. Some patients who respond poorly or are intolerant to other steroids may be managed satisfactorily with dexamethasone. As with all drugs of this class, the disadvantages and dangers, particularly since there is a tendency toward repeated use, should be weighed carefully against the benefit to be expected. Prolonged therapy with dexamethasone will suppress the function of the adrenal cortex; although ordinarily a hazard to its use, this property of the drug may be used advantageously in patients with adrenogenital syndrome.

Toxicity and Side-Effects.—Although clinical experience is not sufficient to permit quantitative comparisons, it is apparent that side-effects and untoward reactions to dexamethasone are qualitatively similar to those of other gluco-corticoids. It would appear from available data that dexamethasone has less tendency to cause salt and water retention and disturbance of glucose metabolism. The drug can cause peptic ulceration, decreased resistance to infection, demineralization of bone with resultant osteoporosis, insomnia, psychic disturbances, rounding of the face, fat deposition, hirsutism, acne, abdominal striae, petechiae, purpura, and amenorrhea. In common with all steroids, except triamcinolone which may cause decreased appetite and weight loss, dexamethasone causes an increase in appetite; weight gain may often be observed during prolonged therapy. The euphoria often seen with other steroids and the aggravation of the diabetic state have not been prominent with this drug. Relative contraindications to therapy with dexamethasone include active, latent, or questionably healed tuberculosis, other acute or chronic infections, peptic ulcer, osteoporosis, fresh intestinal anastomoses, diverticulitis, thrombophlebitis, and psychotic tendencies. Herpes simplex of the eye is an absolute contraindication except when the need for dexamethasone is considered greater than the risk to the function of the eye. The drug should be used cautiously in pregnant women, particularly during the first trimester, to avoid the possibility of postnatal hypoadrenalism in the fetus.

Dosage.—Dexamethasone is administered orally. Dosage must be individualized according to the severity of the disease, anticipated duration of steroid therapy, appearance of side-effects, and therapeutic response. In general, the total daily dosage of dexamethasone is about one-fifth that of triamcinolone or methylprednisolone and about one-

sixth that of prednisone or prednisolone. In chronic conditions requiring long-term therapy, the lowest dose that will provide adequate, not necessarily complete, relief of symptoms should be used. This is because prolonged administration of high doses may produce unwanted hormonal effects. In life-threatening and other acute conditions, large doses are permissible and may be mandatory for short periods of time. The daily requirement is usually given in three or four divided doses. However, with the exception of acute conditions, administration of the daily requirement in two divided doses provides adequate therapy for some patients both initially and in maintenance.

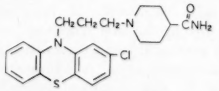
For rheumatoid arthritis, suppressive doses of 1.5 to 3 mg. per day may be given initially. Dosage is then decreased gradually to the smallest amount that gives the desired degree of symptomatic relief; this may be as low as 0.75 mg. per day. Alternatively, therapy may be initiated with small doses (0.75 to 1 mg. per day) and then increased gradually to eventual maintenance levels. For acute, nonfatal conditions such as seasonal asthma and self-limited ocular and dermatological disorders, daily dosages range between 2 and 3 mg. For chronic, potentially fatal diseases such as disseminated lupus erythematosus, pemphigus, and sarcoidosis, the usual initial dose is 2 to 4.5 mg. per day. For acute rheumatic fever, crisis of disseminated lupus erythematosus, and severe allergic reactions, initial doses of 7.5 to 10 mg. or more per day have been used. However, in such acute, life-threatening situations in which rapid onset of action is imperative, consideration should be given to the intravenous use of gluco-corticoids suitable for this route of administration. Massive doses of 10 to 15 mg. per day have been given to patients with acute leukemia, the nephrotic syndrome, and acute pemphigus. For the treatment of adrenogenital syndrome daily doses of 0.5 to 1.5 mg. are used.

Preparations.—tablets 0.5 mg. and 0.75 mg.

Year of introduction: 1958.

Merck Sharp & Dohme Research Laboratories, Division of Merck & Co., Inc., and Schering Corporation cooperated by furnishing scientific data to aid in the evaluation of dexamethasone.

Pipamazine (Mornidine).—10-[3-(4-Carbamoylpiperidino)propyl]-2-chlorphenothiazine.—The structural formula of pipamazine may be represented as follows:



Actions and Uses.—Pipamazine is a substituted phenothiazine derivative with actions similar to those of other drugs of this chemical class. Thus, it exhibits both antiemetic and sedative actions. Pharmacological studies in animals indicate that, on a weight basis, pipamazine may be more potent than chlorpromazine in antiemetic activity but less potent in tranquilizing activity. Such studies suggest a relative specificity or increase in antiemetic action in relation to tranquilizing action. Hence, pipamazine is used clinically only for its antiemetic effects. The drug influences nausea and vomiting by an inhibitory action on the medullary chemoreceptor trigger zone; it does not act on the emetic center. After oral administration in human beings, the onset of action of pipamazine is about 30 minutes.

Pipamazine has been employed for the prevention and control of nausea and vomiting due to a variety of causes. These include emesis associated with pregnancy, anesthesia, radiation therapy, nitrogen mustard therapy, and gastroenteritis. In one controlled study, the drug reduced the incidence of vomiting after surgical anesthesia from 10% to 6%. The remainder of the clinical reports are largely uncontrolled. Nevertheless, it is the clinical impression of most observers that pipamazine is frequently effective for the symptomatic management of nausea and vomiting. Its ultimate usefulness in comparison with other antiemetic agents must await the results of additional controlled studies.

Toxicity and Side-Effects.—Doses greater than 10 mg. per day may, in occasional patients, cause mild to moderate sedation. With the exception of drowsiness, however, and, less frequently, postural hypotension, the usual therapeutic doses of pipamazine are well tolerated. Signs of extrapyramidal involvement (muscle spasm and Parkinson-like symptoms) have been encountered at dosage levels far beyond the usual therapeutic range. In occasional instances, abnormal values in certain liver function tests (serum bilirubin, serum transaminase, and sulfobromophthalein retention) have been observed, but overt jaundice or clinical signs or symptoms suggesting hepatic damage have not been attributed to therapy with the drug. Because it is a phenothiazine derivative, however, pipamazine should not be given to patients with known liver disease. For the same reason, it should be withheld in patients with leukopenia or other evidence of hematopoietic depression, even though there is no evidence that the drug depresses bone marrow function. Since it potentiates the action of other central nervous system depressants, caution is enjoined in the use of pipamazine in patients under the influence of narcotics, barbiturates, alcohol, or general anesthetics. Chronic administration in rats causes arrest of the estrous cycle in the progestational phase and reduction of weight of accessory reproductive organs in both sexes; the clinical significance of these laboratory findings is not known, but it might be important.

Dosage.—Pipamazine is administered orally or by intramuscular or intravenous injection. The usual dose for adults by the oral route is 5 mg. every four to six hours; if the drug cannot be retained orally,

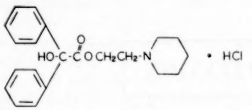
the same dose may be given intramuscularly. If intravenous administration is necessary, a dose of 5 mg. is injected slowly over a period of five minutes.

Preparations.—solution (injection) 5 mg. in 1 cc.; tablets 5 mg.

Year of introduction: 1959.

G. D. Searle & Co. cooperated by furnishing scientific data to aid in the evaluation of pipamazine.

Pipethanate Hydrochloride (Sycotrol).—2-(1-Piperidino) ethyl benzilate hydrochloride.—The structural formula of pipethanate hydrochloride may be represented as follows:



Actions and Uses.—Pipethanate hydrochloride, closely related in chemical structure to benactyzine hydrochloride, is proposed for use in the management of anxiety and tension accompanied by somatic complaints. It has been reported to be helpful in alleviating cardiac symptoms associated with anxiety, including palpitation, tachycardia, and angina; in the management of peptic ulcer, colitis, spastic colon, hypertension, coronary insufficiency, and menopausal complaints; and in ameliorating the tremors of senility and paralysis agitans. However, clinical experience with the drug is still extremely limited, and careful observations comparing it with other similar agents or with placebos have not been reported. Consequently, although favorable results have been described in the aforementioned conditions, further controlled clinical studies are required for convincing evidence that these results were attributable to the drug or that other drugs might not have given equally good or superior results.

In animals the drug has been shown to exert anticholinergic effects and to modify stress-induced behavior in a manner similar to that of benactyzine hydrochloride. It should be pointed out, however, that if the potency ratios observed in animals prevail in man, usual clinical doses of pipethanate hydrochloride would be expected to provide significantly less anticholinergic activity than customary doses of atropine and to influence behavior to a lesser degree than the usual doses of benactyzine hydrochloride. Pipethanate hydrochloride also possesses potent local anesthetic and quinidine-like atrial antifibrillatory actions, but these properties, demonstrated in the laboratory, have received no clinical application.

Although toxicity studies in animals are inadequate as reported, no undesirable effects, with the exception of drowsiness, have been reported in man. The possibility of serious systemic toxicity, however, has not been thoroughly explored either in animals or in human subjects. Therefore, patients receiving the drug should be carefully observed for untoward effects.

Dosage.—Pipethanate hydrochloride is administered orally. The proposed dose is 3 to 6 mg., three times daily.

Preparations.—tablets 3 mg.

Year of introduction: 1959.

Reed & Carnrick cooperated by furnishing scientific data to aid in the evaluation of pipethanate hydrochloride.

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COUNCIL ON INDUSTRIAL HEALTH

The following statement, prepared by the Committee on Industrial Health Emergencies of the Council on Industrial Health, has been approved by the Board of Trustees of the American Medical Association.

B. DIXON HOLLAND, M.D., *Secretary.*

GUIDE FOR INDUSTRIAL IMMUNIZATION PROGRAMS

Health maintenance is primarily the responsibility of the individual person; however, the employer has an obligation to provide a safe work environment for his employees, and he has a valid interest in the prevention of loss of work time and of work efficiency from his employees' ill health. Definitive diagnosis and therapy of nonoccupational injury or illness is not a responsibility of the employer; but he may provide certain preventive health measures in a given situation where the employee, the employer, and the community stand to benefit. While it is impossible to foresee every situation which might occur locally where an employer might properly make immunization procedures available to his employees, the following principles are offered as a guide.

1. Toward fulfillment of his obligation to provide a safe work environment, or to take appropriate precautionary measures, an employer should pro-

Committee members are Norvin C. Kiefer, Ch., New York; Cortez F. Enloe Jr., New York; Allan J. Fleming, Wilmington, Del.; John N. Gallivan, East Hartford, Conn.; James H. Lade, Albany, N. Y.; Eugene Walsh, Chicago; and Lee N. Hames, Secretary, Chicago.

vide immunization procedures to employees who, by reason of their occupation or job assignment, may be exposed to significant hazards against which immunization procedures are available.

2. In keeping with his legitimate right to operate efficiently and profitably in a free enterprise system, with his responsibility to the community, and in demonstration of his good corporate citizenship and concern over his employees' health, an employer may provide immunization procedures in the face of an impending epidemic which threatens to disable so large a proportion of his employees as to interfere materially with operations and against which immunization procedures could not be applied by community health resources in a short enough period of time to afford the optimum protection. The component medical society's approval of company immunization programs conducted under these circumstances should be sought, and to the extent feasible and practicable local physicians should be afforded an opportunity to participate in them.

3. Additionally, an employer may wish to participate in community-wide immunization programs at the request of and in cooperation with a local medical society and community health agencies.

COMMITTEE ON REHABILITATION

The following report is the fourth in a series of articles which have been authorized for publication by the Committee. The first three appeared in THE JOURNAL *on Oct. 24, Nov. 7, and Nov. 21, 1959, pp. 1107, 1359, and 1694. This series deals with various aspects of rehabilitation which are of interest to physicians.*

RALPH E. DE FOREST, M.D., *Secretary.*

PSYCHIATRIC REHABILITATION

Benjamin Simon, M.D., Arlington Heights, Mass.

World War II marked the beginning of modern psychiatric rehabilitation as we know it today. Occupational therapy had served, almost alone for a century, to supply the need of the psychiatric patient for normal activity and as a means of teaching him some avocation which he could take home as a therapeutic hobby. Other activities such as sports, movies, and music were added in an occasional and unorganized fashion. By default, these activities often came under the direction of the occupational therapist who was the one person with a formal training in paramedical activities and who was recognized as a qualified technician.

With the extensive application of group psychotherapy came the awareness of problems besetting military psychiatric patients—problems involving attitudes toward illness, attitudes of the self to illness and to the attitudes of others, problems of self-esteem, problems of adjustment within the hospital, and problems of adjustment outside the hospital. These concerns were personal, social, and economic; they included problems of relationships with parents, spouse, the Army, the community, and employers.

The special character of the psychiatric patient brought these problems out in much stronger relief. Generally, the patients were not confined to bed or suffering from a physical disorder around which their interest centered. On the surface they were not ill. Usually, they were fully ambulatory, with only a small portion of their time and interest devoted to medical treatment, including psychotherapy. The very nature of their emotional disorders involved an enlarged caricature of the general problems of the "normal" medical patient.[1] The rest of the patient's hospitalized time was an empty void, a small portion of which was filled in by occupational therapy. In contrast to the ordinary state hospital filled with psychotic patients with the accompanying management problems, many patients in the Army hospital were not psychotic and were capable of being handled like "normal" persons, as indeed were most of the psychotic patients as well, particularly when under psychiatric treatment.

The major problem in the care of psychiatric disorders seemed then to divide itself into two ill-defined segments: (1) the programming of activities within the hospital and (2) planning for the future and programming in this direction. The ultimate outcome of serious application to these problems was the development of the reconditioning programs including physical activities, handicraft activities, educational activities, music activities, recreational activities, and others as they developed. The continuous scrutiny of these activities which came up in group therapy sessions

Chairman, Committee on Rehabilitation, American Psychiatric Association.

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served eventually to develop the general principles of rehabilitation which the Army called "reconditioning."

Psychiatric rehabilitation has been variously defined, and opinions still differ. In the "American Illustrated Medical Dictionary" [2] it is defined as "The restoration to useful activity of individuals who have been wounded so as to suffer from physical or emotional disability, such restoration including treatment of the disability and training to fit the individual for occupation in industry." Other dictionary definitions place even more emphasis on restoration to economic productivity. The Commission on Chronic Illness [3] defines rehabilitation as "The restoration of the handicapped to the fullest physical, mental, social, vocational, and economic usefulness of which they are capable." The range of services was classified into three principal areas: (1) medical—medical and psychiatric diagnosis and treatment, together with such supportive services as physical therapy, occupational therapy, speech therapy, and nursing care; (2) psychosocial—social and psychological evaluation, social casework, and personal counseling; and (3) vocational—prevocational evaluation and experience, vocational counseling, graduated physical preparation and hardening, vocational training, trial or permanent employment in a sheltered workshop, and selective placement in employment.

Some have quarreled with these definitions and have felt that they did not include, for example, the work with mentally retarded or chronic mental patients who had never attained a reasonable level of social adjustment prior to the illness. It would seem that, while the term "habilitation" might be applicable to these, there is no real need to be so specious if we consider that the object is to attain the fullest adjustment of which any person is capable.

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Therapeutic Use of the Self

The concept of the "therapeutic use of the self" applies to all persons (including physicians) who stand in a professional relationship to mental patients, even though such persons may not be practicing psychiatry in its restricted sense. The Committee on Psychiatric Nursing of the Group for the Advancement of Psychiatry crystallized this idea in the article "Therapeutic Use of the Self—A Concept for Teaching Patient Care." [4] The introduction to the article sets forth useful and important guiding principles which, when paraphrased, call for the following things: (1) an understanding of the behavior of the mentally ill patient and an appropriate response to it by all personnel to assure effectiveness in the day-by-day care of the patient; (2) a better recognition of the patient's emotional needs, awareness, and the use by personnel of supporting and corrective responses to his emotional needs, including an appreciation of some aspects of interaction between patient and nurse and its meaning and application in the therapeutic effort; (3) the hospital to serve as a smaller, limited world wherein new experiences in living and new personal relationships produce minimal anxiety and maximal support so that the patient gradually may be helped to feel that living with others is less threatening and a less forbidding experience. This is necessary since a patient enters a psychiatric hospital because he has experienced difficulties in living in the outside world. Whatever the nature and expression of these difficulties, they invariably include a breakdown in relationship with other people; (4) a hospital program which enables the patient to learn to live more effectively with other people. Every mental illness includes the problem of the patient's particular way of relating himself to others and of participating with others in activities. When a patient enters a mental hospital, he has already established patterns of behavior intended to facilitate his withdrawal from anxiety-provoking relationships. Withdrawal may be variously expressed. In the attempt to cope with his anxiety, the patient chooses that form of expression which, in his experience, has been most effective in maintaining distance from others for his subjective comfort; (5) personal relationships which gratify the patient's needs, facilitate his communication with others, and enhance his social participation. If these relationships remain essentially therapeutic, the patient-personnel relationship can become an integral part of the whole therapeutic regimen. It is important for personnel to understand and to be aware of the feelings, thoughts, and actions of the patients. They should have a similar understanding of their own thoughts and actions in any situation. Such awareness is acquired gradually and depends upon collaboration with the psychiatrist, conferences with supervisors and co-workers, and repeated experiences with patients.

Although these principles were originally intended for "nursing personnel," it became quite apparent that this philosophy of patient care extended through all the areas in which patients were related to personnel and that this was especially applicable to personnel in the so-called rehabilitation services.

The Psychiatric Hospital, the Community, and the Patient

There has been a very strong shift from concern with the activity, or modality, to the psychodynamics of the personal relationship. Emphasis is now predominantly on the needs of the patient as a whole person; the modality used has become the focus about which the relationship may develop and progress. This has significantly changed the conception of the psychiatric hospital which is now becoming the "open hospital" and the "therapeutic community."[5] The "open hospital" repeatedly

underscored the increasing need for patient activities and relationship with personnel in all categories. Architectural planning for hospitals also had to be reconsidered in the light of this new approach to rehabilitation. These aspects have been discussed by Martin,[6] Simon,[7] and others.

The Patient's Adaptation

Rehabilitation today clearly includes every aspect of the treatment of the whole person. This is pictured by Greenblatt [8] (fig. 1) as a function of the individual's adaptation to six essential areas of living: psychological, vocational, family, sociorecreational, educational, and community. Throughout life, the patient tries to increase his "life space" against internal or external resistance. Success in all areas is represented, diagrammatically, in terms of an equilateral hexagon. In terms of this model, deficiencies or imbalance in any given area can produce a variety of asymmetrical hexagons.

The disturbance in the symmetry of the rehabilitation "life space" of course will antedate hospitalization and will determine the type of help which the patient must have in the various areas of living.

In the attempts to solve the many difficulties in readaptation of the patient to the community, many modifications in hospital organization and procedure developed. One of the earliest was the Family Care Program. Historically, the earliest was the famous Gheel Colony, the prototype of the family care program of the state hospital. There is now a large number of agencies and programs designed to implement the transitional phase of the patient's return to the community, where he cannot return directly. The impact of rehabilitation

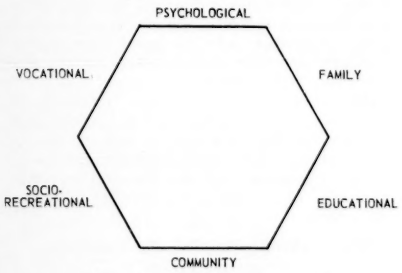

Fig. 1.—The rehabilitation "life space."

in the newer sense has resulted in the establishment of such transitional agencies and institutions as the Altro Rehabilitation Centers, halfway houses like Portals and the Vermont Center,[6b] social-therapeutic clubs like Fountain House, after-care clinics, and changes in the hospital, giving it a more participant role in the community life of the patient. The day and night hospitals are examples of this.

Greenblatt [8] pictured the transitional steps of the patient's return to the community from the hospital in a staircase (fig. 2), which includes all available resources in which, as an individual, each patient follows his own pattern. No given order of steps could be considered as satisfactory for all patients.

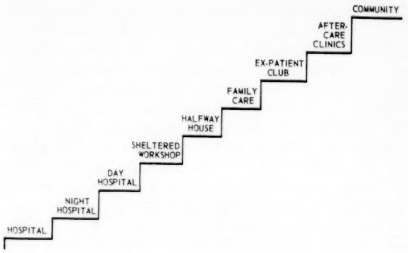

Fig. 2.—Transitional steps in patient's return to community.

The Hospital and Community

As one surveys this movement of patients, it is apparent that there is a continuum of movement, not only from the hospital to the community but from the community to the hospital. These various rehabilitation facilities and agencies may play a role in the prevention of hospitalization as a stage short of hospitalization to which the patient may temporarily regress for further help in continuing in the community. From this point of view, then, the hospital program and the community are integrated into one, with a continuum of psychiatric service going "upstairs" or "downstairs," as may be necessary. Clearly, the leadership should lie with the medical staff in the hospital, and it should play an important role in the organization and direction of the total program. The hospital service now truly fulfills its role as stated earlier—both as an extension of the community and as a model of the community—the "open hospital" and the "therapeutic community." In a similar sense, the community becomes a model of the ideal hospital and, through its agencies, performs for those of its citizens who need it the functions of the many rehabilitation divisions of the hospital itself. It is clear that the rehabilitation of the patient now really begins before his hospitalization, and therapy and practice should be under way in the hospital without delay. No longer is it a procedure to be employed when the patient is "ready to go home." The boundaries between home, community, and hospital have blurred.

Of ever-increasing importance will be the role of the family physician in the community as the "medical" part of the community program. To this end, there has been an increasing number of sem-

inars and classes for general practitioners, in addition to development of closer relationship between hospitals and physicians in the community.[8]

Homemaker services to care for the family of a patient during the period of hospitalization, in close coordination with the care of the patient, have become increasingly effective.[9]

In the same manner in which the community physician is becoming an extension of the hospital in the community, so the hospital physician is being encouraged now to be an active member of the community without the hospital as well—to the end that the mental hospital of today and in the future will be truly a community mental hospital.

Summary

The concept of rehabilitation of the psychiatric patient in the last decade has extended far beyond the simple dictionary definition of the term. The four major trends which stand out today are (1) the "open hospital" and the "therapeutic community," which have created the need for the great increase in rehabilitation services, the increased close relationship of the hospital with the community, and the establishment of the hospital as an integral part of the community; (2) the application of psychodynamics embodied in the "therapeutic use of the self"; (3) the development of a great variety of transitional agencies between community and hospital for the implementation of a program built around the person as a psychological whole. The need for integration and direction of the total program in the interests of the whole person is apparent. If these programs are developed, the need for education and training of both professional personnel and nonprofessional volunteer personnel becomes apparent. The need for good organization and coordination is obvious. This is true not only within the hospital setting, where there is a growing category of rehabilitation coordinators (coordinators of adjunctive therapies),[10] but in the coordination of community activities as well. In this respect, the community physicians will play an important role both in the coordination of activities and in direct assistance to the various rehabilitation units and organizations; and (4) the establishment of the mental hospital as a true "community hospital" with an "open door" through which hospital personnel, from the medical staff on, are encouraged to make themselves a part of the community and through which the physicians of the community, psychiatrists and nonpsychiatrists, are encouraged to make themselves a part of the hospital.[11]

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TRANSMISSION OF INFECTIOUS HEPATITIS.—Since the nineteenth century there have been epidemics of jaundice that have been attributed to water-borne transmission. The evidence accumulated in recent years is sufficiently complete to warrant recognition of this mode of spread of infectious hepatitis as an epidemiologic entity. In this regard, infectious hepatitis is the first viral disease for which a water-borne route of infection has been generally accepted. Such a route has been postulated for poliomyelitis, but no studies have been reported in which conclusive evidence was obtained. It is believed that person-to-person contact is the most frequent type of transmission of infectious hepatitis and there is no evidence to the contrary at the present time. It is important to recognize, however, that it is difficult to establish the water-borne route of infection, and it may account for more cases than can be demonstrated by available methods.—J. W. Mosley, M.D., Water-Borne Infectious Hepatitis, *The New England Journal of Medicine*, Oct. 1, 1959.

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YOUNG TURKS—OLD TURKS

IT IS gratifying to discover that sophistication in clinical investigation, which is almost synonymous with academic medicine, does not necessarily scorn the romantic. At least the emotional tropism that draws us to an institution or to an organization may be powerful enough to counteract any stigma of sentimentalism when one is assigned the honor of assembling the chronicles of such an organization, so that the present will not forget the past. In a recent issue of the *Journal of Clinical Investigation* (special issue, **38**:1783-1878, Oct. [pt. 2] 1959), a special supplement edited by Ellen R. Brainard was devoted exclusively to a recounting of significant events in the formation, early days of struggle, and rapid development of a coterie of clinical investigators into a community of scholars known as the American Society for Clinical Investigation—the Young Turks.

The person responsible for the idea was Dr. Samuel J. Meltzer, Russian-born and German-trained, a transatlantic ship's doctor until he was attracted permanently to the United States in 1883. At the age of 53 he abandoned a lucrative practice of medicine in Harlem to become associated with the newly established Rockefeller Institute for Medical Research. For some time the eponym for the American Society for Clinical Investigation was the Meltzer Verein, in honor of this distinguished scientist and in deference to his Teutonic training. According to the best recollection, the idea for the society was founded on the boardwalk in Atlantic City, after a session of the American Medical Association in 1907. The first meeting of the society occurred two years later. The members were identified as Young Turks to emphasize the revolt against the Association of American Physicians, the Old Turks. The prevailing sentiment in the founding of the American Society for Clinical Investigation was the unwritten pledge to foster the evolution of the young investigators into wise professors of our medical faculties. Just 15 years after the society was founded the first issue of their periodical, the *Journal of Clinical Investigation*, was published.

Concomitant with the compilations of the history of the Young Turks, two Old Turks in formal academic, but not intellectual, retirement have been laboring to bring up-to-date the records for their respective corporate structures. Dr. J. Howard Means, one-time Jackson professor of medicine at Harvard Medical School, one-time member of the editorial board of the *A. M. A. Archives of Internal Medicine*, and one-time president of the Association of American Physicians, is preparing the history of the association during its 75 years of growth. Also, Dr. C. Sidney Burwell, one-time dean of Harvard Medical School and one-time professor of research medicine at Harvard, is compiling a history of this institution of learning for the first half of the current century. It is suspected that there will be considerable overlapping in persons and projects in these three significant documents.

The American Society for Clinical Investigation has a composition of about 275 active members. Many of the Young Turks in the original roster remained in clinical investigation and, by the time their turn came for graduation to Old Turks, were elected to membership in the Association of American Physicians. The current panel of emeritus members of the society contains the names of almost 300 physicians and medical scientists. Last, the history of the society lists almost 150 Old Turks who have joined their patients. Whether active, emeritus, or in the third category whose activity remains unknown, the vast majority have been dedicated to research, the pursuit of clinical investigation, and the teaching of the art as well as the science of medicine to pregraduate and to postgraduate disciples.

To paraphrase A. Lincoln, the world will soon forget what is said here but it will long remember what they did here. There are several Nobel laureates on the registry of the society. The deans of medical schools are as abundant as the seeds in a watermelon, while the number of professors in medical schools are as "thick as autumnal leaves that strow the brooks in Vallombrosa." Whether one looks kindly or not on those who pursue investigation and are dedicated simultaneously to bedside teaching, this conclusion seems inescapable: The inventory of Young Turks and Old Turks is intrinsic to the tremendous progress in the art and practice of medicine in America since the beginning of

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this century. The history of the Society of Clinical Investigation is an intriguing document. We await with anticipation a similar volume of the Society of Old Turks as well as the history of the last half-century of the Harvard Medical School, where so many teachers of medicine received a modicum or a significant portion of their formal professional education.

BIOCHEMICAL ASPECTS OF ERYTHROCYTE FORMATION

The mature erythrocyte consists of about 90% hemoglobin by dry weight; the remainder is stroma and an impressive array of enzymes. Some of these enzymes are concerned with oxygen and carbon dioxide transport while others may be vestiges of previous existence as a cell capable of division. Recent investigations have contributed to the understanding of the mechanisms involved in biosynthesis of various components of the red blood cell. Interest has been focused principally on the manner of hemoglobin synthesis.

Understanding of the biochemistry of heme synthesis had its inception in the discovery of Shemin and Rittenberg [1] that glycine labeled with isotopic nitrogen (N^{15}) administered to animals gives rise to erythrocyte heme containing N^{15}. With this observation as the foundation almost the entire biosynthetic pathway of heme has been elucidated. Rapid advances in this field followed quickly upon the finding by Shemin and his colleagues [2] and by investigators in England that heme synthesis could be studied in vitro with use of avian erythrocytes, reticulocytes, or hemolyzates of these cells. The well-documented sequence of reactions by which heme is formed is as follows.

Glycine condenses with an activated succinate derivative (probably succinyl coenzyme A), to yield α-amino-β-keto adipic acid which either enzymatically or spontaneously loses a carboxyl group to become δ-amino levulinic acid. Two molecules of δ-amino levulinic acid condense to form the pyrrole, porphobilinogen. The enzyme carrying out this condensation appears to be a copper-containing, sulfhydryl enzyme. The detailed mechanism of how four phorphobilinogen molecules condense, lose six carboxyl groups, and form two double bonds in the side chains resulting in protoporphyrin is still not clear. It seems probable that uroporphyrin and coproporphyrin (containing eight and six carboxyl groups, respectively) are not direct precursors but are formed from intermediates which also yield protoporphyrin. The more direct precursors may be the porphyrinogens, i. e., the reduced forms of the porphyrins.

There is still doubt concerning the step at which the iron is incorporated into the molecule. Experiments with chicken erythrocyte hemolyzates have shown the possibility of an enzymic reaction between ferrous iron and protoporphyrin to yield heme. This reaction also occurs nonenzymically. Evidence derived from experiments with liver mitochondria substantiates the enzymic pathway. It is not certain whether the iron is derived from ferritin or directly from transferrin (siderophilin). The mechanism of reduction of the ferric to the ferrous form needs to be clarified.

The other part of the hemoglobin molecule, globin, has been the subject of intensive study [3] as one example of protein synthesis. It appears likely that globin is formed by the same type of reaction sequence as are other proteins. The process by which globin is linked to heme is uncertain, although model experiments have shown that analogous reactions occur spontaneously.

Under normal conditions the formation of globin and of heme keep pace with each other so that no accumulation occurs of either excess porphyrin or protein. The mechanism of this fine degree of regulation poses an interesting, important, and as yet unsolved problem.

The biochemical role of cyanocobalamine (vitamine B_{12}), which has such a striking effect in restoring normal maturation of erythroid cells in pernicious anemia, has not been established. Since vitamins, at least those whose chemical functions are understood, are constituents of coenzymes, attempts have been made to find a coenzymic role for this vitamin. Reports have appeared of the participation of cyanocobalamine in reactions involving deoxyriboside formation, incorporation of amino acids into proteins, reduction of the hydroxymethyl group of serine and transfer to homocystine to form methionine, and in the formation of the methyl group of thymine. None of these reactions accounts for the high degree of specificity of the maturation arrest characteristic of pernicious anemia and the dramatic release of this maturation arrest by minute amounts of the vitamin.

In the last few years evidence has accumulated which firmly establishes the hypothesis of Carnot [4] indicating the existence of a hormone which regulates erythropoiesis. This factor, erythropoietin (hematopoietin, hemopoietine) appears in small amounts in normal blood and in elevated amounts in response to either anemic anoxia or anoxic anoxia in many species, including man. The administration of cobaltous chloride to experimental animals also

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results in increased plasma titers of erythropoietin. This finding probably explains the polycythemia-producing effect of cobalt. While it has not yet been completely purified, this hormone is apparently a glycoprotein. It is relatively heat and acid stable but is inactivated by proteolytic enzymes.

There is evidence indicating that in the experimental animal erythropoietin is formed in the kidney. Such an origin for erythropoietin may serve to explain the anemias associated with renal disease and the polycythemia sometimes present in conjunction with hypernephroma. There have been no reports of the use of erythropoietin in the treatment of anemias in man.

SMOKING AND LUNG CANCER

A summary of pertinent data relating to smoking and lung cancer appeared in THE JOURNAL, Nov. 28, pages 1829 to 1837. Written by Dr. Leroy E. Burney, surgeon general of the Public Health Service, the report documents the major researches and identifies the Public Health Service with those who consider that the evidence to date implicates smoking as the principal etiological factor in the increase in lung cancer. A number of authorities who have examined the same evidence cited by Dr. Burney do not agree with his conclusions. Although the studies reveal a relationship between cigarette smoking and cancer that seems more than coincidental, they do not explain why, even when smoking patterns are the same, case rates are higher among men than among women and among urban than among rural populations. Neither the proponents nor the opponents of the smoking theory have sufficient evidence to warrant the assumption of an all-or-none authoritative position. Until definitive studies are forthcoming, the physician can fulfill his responsibility by watching the situation closely, keeping courant of the facts, and advising his patients on the basis of his appraisal of those facts. The Public Health Service can best meet its obligations by collecting and disseminating data from all sources and making known to the health and medical professions its own evaluations of such data.

J. H. T.

MEDICAL FILM REVIEWS

Circulation of the Blood: 16 mm., color, sound, showing time 7 minutes. Produced in 1958 by Churchill Wexler Film Productions, Los Angeles. Procurable on loan or purchase from American Heart Association Film Library, 267 W. 25th St., New York 1.

This film, by means of diagrammatic drawings, shows how the heart works and explains the structure of the arteries and how their expansion and contraction controls the flow of blood. Animated diagrams trace the circulation of the blood through the body. This is a stylized, accurate, and attractive presentation of the activity of the normal human heart. The animated diagrams are augmented by a few actual views of the movement of blood in capillaries, arterioles, and venules, and the animation and narration are excellent. The film is highly recommended for adult lay groups and also for supplementary material in college and high school classes in biology, physiology, and health education.

Physical Examination of the Newborn: The Art and the Findings: 16 mm., color, sound, showing time 33 minutes. Prepared by Mary B. Olney, M.D., San Francisco. Produced in 1959 by Medical Arts Productions, San Francisco for and procurable on loan from Pfizer Laboratories, 630 Flushing Ave., Brooklyn 6, N. Y.

Part 1 of this film demonstrates the steps of a complete routine examination as it is performed on a baby a few hours old. Part 2 shows special examination techniques and some of the more common abnormal findings as well as normal findings which can be mistaken for anomalies. One of the best parts of this film is the last sequence, in which the pediatrician visits the mother with the newborn infant and demonstrates to her many of the points in the physiology of newborn infants which might possibly disturb her. This is a very good illustration of putting a mother at ease with her newborn baby. This film is an excellent demonstration of physical examination of newborn infants and it is highly recommended for obstetricians, pediatricians, general practitioners, and house officers.

The Thiersch Wiring For Massive Rectal Prolapse: 16 mm., color, sound, showing time 15 minutes. Prepared in 1958 by and procurable on loan from Robert Turell, M.D., 25 E. 83rd St., New York 28.

This film demonstrates the technique of inserting a Thiersch wire for the control of rectal prolapse. The author's indications for using this procedure, as well as his program of preoperative and postoperative care, are described. Photographs demonstrate the condition of patients before and after the operation and roentgenograms are shown of the wires in place after surgery. Some of the complications of this operation are described; however, a rather common one, fecal impaction, has been omitted. The technical details are well presented, but one must look at the indications for this procedure with a very critical eye. The photography is good and the film will be of interest to proctologists.

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MEDICAL NEWS

ARKANSAS

Student Building Dedicated.—The Jeff Banks Student Union Building at the University of Arkansas Medical Center, Little Rock, was dedicated Nov. 20 to the memory of the late Dr. Jeff Banks, former head of the School of Medicine anatomy department. The ceremony also officially opened the medical center's new Residence Hall which has been occupied by students since the start of the 1959-1960 school term. Construction on the two buildings, financed by the federal government, was completed this summer. The Residence Hall is a 10-story facility to accommodate 315 single students and 95 married couples in efficiency apartments. The Student Union contains the main lounge, coffee shop, recreation room, barbershop, music room, and administrative offices. Dr. James D. Mashburn, of Fayetteville, responded to the dedication for the Jeff Banks Memorial Student Aid Fund. The fund was started to help finance the education of needy and deserving students in the School of Medicine.

CONNECTICUT

Visiting Professors.—Dr. William C. Gibson, Kinsman Professor of Neurological Research at the University of British Columbia, will be visiting professor of the history of medicine at the Yale University School of Medicine, New Haven. Dr. Horst Bickel was appointed visiting associate professor of pediatrics at Yale from August to November. He has been assistant professor at the University Children's Hospital, Marburg an der Lahn, Germany, since 1954. Dr. Bickel is participating in the teaching activities of the department of pediatrics and continuing his research in inborn errors of metabolism. During the current academic year, Noah Lichtenstein, Dr. Phil., will serve as a visiting associate professor of biochemistry. Since 1954, he has been associate professor of biochemistry at the Hebrew University in Jerusalem. While at Yale, he will participate in graduate seminars and teaching of the first-year medical students.

ILLINOIS

Clinics for Crippled Children.—Clinics for physically handicapped children in Illinois have been scheduled by the University of Illinois, Division of Services for Crippled Children. Fifteen general clinics were scheduled for December providing diagnostic orthopedic, speech, and hearing examination along with medical, social, and nursing service. Any physician may refer to a convenient clinic any child for whom he may want examination or consultative services. The last seven clinics in December will be as follows:

Dec. 15—Belleville, St. Elizabeth's Hospital.
Dec. 15—Effingham (rheumatic fever), St. Anthony Hospital.
Dec. 15—Peoria, Children's Hospital.
Dec. 16—Chicago Heights (general), St. James Hospital.
Dec. 17—Bloomington, St. Joseph's Hospital.
Dec. 17—Elmhurst, Memorial Hospital of DuPage County.
Dec. 17—Rockford, Rockford Memorial Hospital.

Chicago

Dr. Stollerman to Speak at Joint Meeting.—There will be a joint meeting of the Chicago Society of Internal Medicine and the Scientific Section of the Chicago Heart Association Dec. 14, 8 p. m., at the Drake Hotel. Dr. Gene H. Stollerman, associate professor of medicine, Northwestern University Medical School, will present "The Problem of Streptococcal Immunity in Rheumatic Fever Prevention." A dinner will precede the meeting which is open to all. For information, write Mr. Walter A. Rambach, Secretary, 720 N. Michigan Ave., Chicago 11 (Telephone: WH 4-0944).

Dr. Atkinson to Lecture at Ophthalmological Meeting.—Dr. Walter S. Atkinson, Watertown, N. Y., will present "Development of Ophthalmic Anesthesia" as the 16th annual Gifford Memorial Lecture at the 12th annual clinical conference of the Chicago Ophthalmological Society Feb. 12, 5:15 p. m., at the Drake Hotel. Subjects to be considered during the meeting Feb. 12-13 are as follows:

Symposium on Retinal Disorders.
Ophthalmodynamometry in Intracranial Vascular Disease.
Observations of Cataract Surgery.
Ultrasonography in Clinical Ophthalmology.
Photocoagulation of Iris and Retina.
A New Surgical Approach to Lacrimation Problems.
A Neurosurgeon Looks at Ophthalmology.
Ligament of Wieger.

The registration fee of $45 includes round-table luncheons and a dinner following the Gifford Lecture. For information, write Mrs. Mary E. Ryan, 1150 N. Lorel Ave., Chicago 51.

INDIANA

Program for Training in Family Practice.—A two-year educational program for young physicians aspiring to the role of family doctor and desiring

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

more clinical experience than a routine hospital internship has been developed by the Indiana University School of Medicine. The new family practice program follows suggestions of the American Medical Association and the American Academy of General Practice for such training but differs from similar programs now offered. The training period will consist of three divisions: The purpose of the first division is to familiarize the trainee with the functioning of those services in which he is later to work in a progressively more responsible capacity. It will consist of experience in the emergency room, medicine, pediatric, psychiatric, obstetrical, and gynecological services. The second division will encompass advanced experience in medicine and pediatrics. The third division will consist of elective work. The stipend is $2,400 for the first year and $2,700 for the second year. In addition, the trainee will enjoy all the privileges extended to the other members of the house staff. There are to be three appointments a year, and the selection is to be through the regular procedure of the Intern Matching Program. For information and applications, write to the Office of the Medical Director, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

KENTUCKY

Meeting of Surgeons in Louisville.—The American College of Surgeons will hold a sectional meeting Jan. 21-23 in Louisville. Headquarters will be the Brown Hotel. Dr. Rudolf J. Noer, of the University of Louisville School of Medicine, is chairman of the advisory committee on local arrangements. In addition to the general surgery program of particular interest to gynecologists, thoracic surgeons, vascular surgeons, and urologists, a special two-day ophthalmic surgery program, a special two-day program for otolaryngologists, and a cancer program workshop for medical directors of approved cancer programs are planned. Dr. Ernest C. Strode, Lexington, president of the Kentucky chapter of the college, will preside over the afternoon general surgery program, Jan. 21. Clinics will be held Jan. 23 at Louisville General Hospital. Medical motion pictures will be shown during the three days. Dr. H. Prather Saunders, associate director, The American College of Surgeons, 40 E. Erie St., Chicago 11, is in charge of all sectional meetings for the college.

MARYLAND

Rabies in a Bat.—Dr. Charlotte Silverman, Baltimore, of the Maryland State Department of Health, supplied a report from Dr. Charles L. Wisseman Jr., University of Maryland, Baltimore, of a suspected case of rabies in a bat, the first to be reported in Maryland. The bat was found fluttering erratically close to the ground in a residential area in Baltimore County. The bat was killed by a group of children and then abandoned. It was identified as the hoary bat, *Lasiurus cinereus*. Mouse-inoculation tests were performed and the first deaths occurred in the mice 21 days after the inoculation. Two additional mouse passages were done and the incubation period remained from 15 to 20 days. Smears prepared from the bat's brain revealed inclusion bodies suggestive, but not entirely typical, of Negri bodies. Fairly typical Negri bodies have been found in smears taken from the brains of the mice.

Hospital Plans to Move.—Sinai Hospital of Baltimore, Inc. plans to move from its present location at Monument Street and Rutland Avenue to its new quarters at Belvedere Avenue at Greenspring on Dec. 13, when some 150 to 200 patients will be transported to the new location. Located on a 50-acre site in northwest Baltimore, the new facilities of the hospital consist of 483 beds and 91 bassinets. Built at a cost of 20 million dollars, it includes a separate Research Building, Medical Staff Residence, School of Nursing, and Nurses' Residence. The expanded outpatient and emergency room facilities are designed to handle 100,000 outpatient visits a year. There are 19 ward beds with no more than two patients to a room, excepting in pediatrics. All patient areas are air-conditioned. The teaching and research program will remain in close association with Johns Hopkins University. A special scientific dedication is planned for Saturday and Sunday, April 23-24, 1960.

MICHIGAN

Lectures in Medical Psychology.—Dr. John I. Nurnberger, of Indiana University School of Medicine, Bloomington–Indianapolis, will deliver the Aquinas College Lectures in Medical Psychology for 1960 at the Aquinas College, Grand Rapids, on Wednesday, Feb. 24. Dr. Nurnberger, director of the Institute of Psychiatric Research at Indiana University, will speak once in the afternoon and again in the evening. A dinner in the college dining room will be served between the two lectures. In his first lecture Dr. Nurnberger will discuss sex and psychotherapy. His second lecture will be devoted to a discussion of the major manifestations of mental and emotional disorders as a guide to rapid diagnostic appraisal. Admission to the lectures will be limited to physicians.

Conference on Comparative Medicine.—The first annual Michigan Conference on Comparative Medicine will be held March 21-22, at the Kellogg Center for Continuing Education, Michigan State University, East Lansing. This conference will be sponsored jointly by the Michigan Department of Health, the University of Michigan Medical School, the Wayne State University College of Medicine, and the College of Veterinary Medicine at Michi-

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gan State University. Speakers on the program will include Dr. Jacob Furth, Roswell Park Memorial Institute, Buffalo; Dr. William L. Simpson, director, Detroit Institute of Cancer Research; B. R. Burmester, D.V.M., U. S. Regional Poultry Research Laboratory, East Lansing; W. E. Heston, Ph.D., head, General Biology Section, National Cancer Institute, Bethesda, Md., and Dr. Ludwik Gross, chief, Cancer Research Unit, Veterans Administration Hospital, Bronx, N. Y. Address inquiries to Mr. Clayton H. Wells, Conference Consultant, Kellogg Center for Continuing Education, Michigan State University, East Lansing, Mich.

MINNESOTA

Dr. Lundy Honored.—Some 75 former residents gathered at the Mayo Clinic in Rochester, Oct. 10, to honor Dr. John S. Lundy who retired after nearly 36 years of service as chairman of the section on anesthesiology. Dr. Lundy now is on the staff of the Veterans Research Hospital on East Huron Street, Chicago, and a consultant in anesthesia to several hospitals in Chicago.

NEW YORK

Dr. Caccamise Goes to India.—Dr. William C. Caccamise, Rochester, left Nov. 17 to conduct a free eye hospital for the medical missionary nuns of the Kurji Holy Family Hospital in Bihar, India. Dr. Caccamise will return Jan. 17. Some years ago he had conducted a free eye clinic in Bihar, which is 340 miles northwest of Calcutta on the banks of the Ganges River.

Radiation Center in Rochester.—The University of Rochester launched its new $400,000 radiation center at Strong Memorial Hospital, University Medical Center, Oct. 11 with a series of open houses for radiologists, professional people, and the personnel of the University of Rochester Medical Center. The radiation center is designed for diagnosis, therapy, teaching, and research in the problems of cancer and related diseases. Radiation machines include two supervoltage x-ray devices—a two-million electron volt Van de Graaff generating unit and a cobalt rotational unit. The center, housed in its own new building, also has two conventional orthovoltage 250 kilovolt range machines and a 140 kilovolt x-ray generator for treating surperficial lesions. Dr. Philip Rubin, chief of the division of radiation therapy, is director of the radiation center, and Dr. George H. S. Ramsey is chairman of the department of radiology, under which the division functions.

New York City

Vacancies for Radiology Training.—Opportunity for one year training in radiology (there are several vacancies available) with maintenance and honorarium, for anyone interested in learning radiology as an adjunct to his current specialty was announced by Dr. Henry K. Taylor, Roentgenologist, Goldwater Memorial Hospital, Welfare Island 17, N. Y. For information, write Dr. Taylor.

Dr. Rioch to Give Annual Lecture.—The Association for the Advancement of Psychoanalysis announced the eighth annual Karen Horney Lecture will be given by Dr. David McK. Rioch, director, division of neuropsychiatry, Walter Reed Army Institute of Research. The title is "Recent Contributions of Neuropsychiatric Research to the Theory and Practice of Psychotherapy." The meeting will be held on March 23, 8:30 p. m., at Hosack Hall, the New York Academy of Medicine, 2 E. 103rd St., New York City.

OHIO

Dr. Fischer Honored.—Dr. Martin H. Fischer, Cincinnati, was honored at ceremonies Nov. 10, on his 80th birthday. Highlight of the program was the presentation to the University of Cincinnati of an oil portrait of Dr. Fischer, which will hang in the College of Medicine building. Dr. Cecil Striker presented the portrait for the donors and his committee of Cincinnati doctors who studied with Dr. Fischer. Dr. Striker also presented a purse to the university to start a portrait fund for honoring other illustrious medical faculty members.

PENNSYLVANIA

State Medical Election.—Officers of the Pennsylvania Medical Society for 1959-1960 are: president, Dr. Allen W. Cowley, Harrisburg; president-elect, Dr. Thomas W. McCreary, Rochester; first vice-president, Dr. William T. Lampe, Philadelphia; second vice-president, Dr. Stephen J. Deichelmann, Ambler; third vice-president, Dr. John H. Lapsley, Indiana; fourth vice-president, Dr. Dorothy E. Johnson, Philadelphia; secretary, Dr. Harold B. Gardner, Harrisburg; and executive director and treasurer, Mr. Lester H. Perry, 230 State St., Harrisburg.

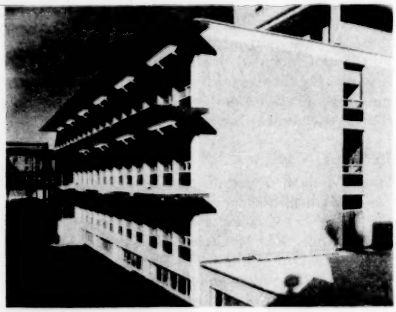
Philadelphia

Dr. Nemir Named Dean.—Dr. Paul Nemir Jr., associate professor of surgery in the University of Pennsylvania's Graduate School of Medicine, and assistant professor of surgical research in the School of Medicine, has been elected dean of the Graduate School of Medicine. He succeeds Dr. George B. Koelle, who resigned to accept the position of chairman of the departments of pharmacology in the School of Medicine and Graduate School of Medicine. Dr. Nemir was a fellow in the Harrison Department of Surgical Research at the University of Pennsylvania School of Medicine 1947-1951, later becoming an assistant professor in the department.

Hospital to Publish Semiannual Journal.—The medical staff of the Germantown Dispensary and Hospital will publish a semiannual scientific journal which will cover scientific material and research projects being carried out at the hospital. The first, to be ready by Jan. 1, will include articles on studies by the cancer research department (some of this work has been aided by the National Institutes of Health), results procured from new drugs which have been tested for pharmaceutical houses and reviewed as to their efficacy in medical practice, and a new approach to older laboratory procedures to reduce the margin of errors in certain situations. The journal will be available to county medical society libraries, as well as major research and diagnostic centers. Dr. Joseph C. Done is editor-in-chief and Dr. Irvin M. Gerson is managing editor.

RHODE ISLAND

Hospital Dedicates New Research Center.—The new George Research Center of the Rhode Island Hospital, Providence, was dedicated on Nov. 1.



The George Research Center of Rhode Island Hospital, Providence.

The three-story white brick and limestone structure for cancer diagnosis, treatment, and research was made possible by a bequest in the will of Daniel F. George, a Providence broker who died in 1949. The $2,100,000 building has no beds, but connecting corridors to the main building and other parts of the hospital facilitate transportation of patients to the cancer center. An auditorium seating 175 occupies part of the first floor. The remainder of this floor has multiple examining rooms and conference rooms. The second floor contains two cobalt treatment rooms, and rooms for superficial and deep x-ray therapy, plus diagnostic laboratories and autopsy rooms. The cancer library and registry are located on the third floor where research laboratories cover a large space. The entire building is air conditioned. Dr. Sidney Farber, professor of pathology, Harvard Medical School, and director of research of the Children's Cancer Research Foundation at Children's Medical Center, Boston, was the principal speaker at the dedicatory exercises.

WISCONSIN

Fraternity Lecture.—The Alpha Psi Chapter of the Phi Delta Epsilon Fraternity at the University of Wisconsin Medical School, Madison, held its lectureship program on Friday, Dec. 11. The guest speaker was Dr. Solomon A. Berson, New York City, chief of the radioisotope service of the Bronx Veterans Administration Hospital. Dr. Berson spoke on the general topic of immunity aspects of insulin resistance and the nature of the insulin-antibody reaction.

WYOMING

Mental Health Clinic in Fremont County.—The first fully tax-supported mental health clinic in the state is being operated in Fremont County. The county is providing half the cost of operating the clinic with the remainder being paid by matching state funds. The city of Sheridan is the only other community to have a regular mental health clinic; however, it is supported by private subscription and matching state funds. Rev. William Watson is president of the Fremont County Mental Health Center, Inc. The clinic corporation is a nonprofit organization, formed to provide mental health services in Fremont County, and is governed by a nine-member board of directors. Clinics will be held in Lander from 8 a. m. to 5 p. m. in the offices of the public health nurse at the county courthouse. Professional staff includes three therapists from the State Training School at Lander. Supervision of the professional staff will be performed by Dr. Jesse E. Simons, State Health Department consulting psychiatrist. Patient fees will be collected to offset the cost of the service, "but no one will be turned away because of inability to pay." Clinic appointments will be limited to children.

GENERAL

Fund Aids Heart Research.—The Life Insurance Medical Research Fund aided 114 different heart research programs in the past year, according to the fund's annual report. In addition, 24 research fellows were supported. Nearly 1.2 million dollars were allocated for these research programs and fellowships, Dr. Francis R. Dieuaide, New York City, scientific director, said. Since 1945, when the fund was organized, its entire resources have been focused on heart disease. Thus far the fund has awarded a total of close to 12 million dollars for heart research programs and fellowships. Financial support comes from a membership of more than 140 life insurance companies in the United States and Canada.

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Grant for Studies in Medical Communication.—The Institute for Advancement of Medical Communication, New York City, has received grant support from the U. S. Public Health Service for three current studies and projects aimed at improving intraprofessional communication in the medical sciences. A program for training investigators to study the general processes by which the results of medical research are disseminated, and by which the informational needs of research workers are met, is being supported by a grant from the National Heart Institute. The division of general medical sciences, National Institutes of Health has awarded a grant to organize the Council of Medical Television. The fate of information evolving from research in the new field of psychopharmacology is being studied under a grant from the National Institute of Mental Health.

Meeting of Ophthalmologists in New York City.—The Institute of Ophthalmology of the Americas will conduct a Post Pan-American Congress meeting at the New York Eye and Ear Infirmary Feb. 9-17. Each symposium will be composed of two Latin-American ophthalmologists and two infirmary staff members. The schedule is as follows:

Feb. 9, 10 a. m.—Cataracts.
Feb. 10, 10 a. m.—Retinal Detachment.
Feb. 11, 10 a. m.—Muscle Anomalies.
Feb. 12, 10 a. m.—Glaucoma.
Feb. 13, 10 a. m.—Uveitis.
Feb. 15, 10 a. m.—Keratectomies and Keratoplasties.
Feb. 16, 10 a. m.—Pleoptics and Macular Function Testing.
Feb. 17, 9 a. m.—Surgical Demonstrations on TV.

Invitations to attend may be obtained by writing to Mrs. Tamar Weber, Registrar, Institute of Ophthalmology of the Americas, New York Eye and Ear Infirmary, 218 Second Ave., New York 3.

Seminar in Reconstructive Nasal Surgery.—A seminar in "Reconstructive Surgery of the Nasal Septum and External Nasal Pyramid" will be held in New Orleans, Feb. 10-13, under the auspices of the department of otolaryngology (Dr. Val Fuchs, chairman), Louisiana State University Medical School and the Charity Hospital. The American Rhinologic Society will cooperate in the presentation. Its founder, Dr. Maurice H. Cottle, professor of otolaryngology, Chicago Medical School, will be the guest director, and Dr. Henry A. Thomas, of L. S. U., will be the executive director. The seminar will offer talks by Dr. Cottle and others who have been invited to participate in an international course to be given in Mexico City, July 4-15, under the auspices of the Escuela Nacional de Medicina e Division del Doctorado, and the American Rhinologic Society. For information, write Dr. Robert M. Hansen, Secretary, American Rhinologic Society, 1735 N. Wheeler Ave., Portland 12, Ore.

Congress of Neurological Surgery.—The second International Congress of Neurological Surgery will be held at the Hotel Statler, Washington, D. C., Oct. 14-20, 1961. This conference is sponsored by the World Federation of Neurosurgical Societies, founded at Brussels in 1955. The first International Congress of Neurological Surgery was held in Brussels in 1957. The federation is presently composed of 25 national neurosurgical societies representing 50 nations. Four morning sessions will be devoted to symposiums on the following topics:

Radioactivity and Heavy Radiation Particles in Neurosurgery.
Space-Occupying Intracranial Lesions.
Reevaluation of Surgery in the Treatment of Pain.
A. Biology of the Nervous System; B. Hydrocephalus.

Voluntary papers are scheduled for presentation in the afternoons. A special feature will be daily television programs of operative procedures and panel discussions on neurosurgical techniques. Correspondence should be sent to Dr. Bronson S. Ray, Secretary-General, 525 E. 68th St., New York 21.

Fellowships in Radiology in Cincinnati.—The department of radiology of the University of Cincinnati College of Medicine and the Cincinnati General Hospital is offering three fellowships. One, in therapeutic radiology for radiologists who have completed their formal residency training, is for one year with a stipend of $6,000. Another fellowship, in radiobiology, radioisotopes, and radiological research techniques, is offered to physicians who have completed their formal residency training and is not restricted to radiologists. The appointment is for one year with a stipend of $6,000. A third fellowship with a stipend of $2,000 is open to physicians who have completed internship or some part of their residency training and is designed to acquaint the fellow with research techniques utilizing radioisotopes and other radiation sources. The latter two fellowships are currently available and new openings will occur on July 1, 1960. Interested physicians should communicate with the Department of Radiology, University of Cincinnati College of Medicine, General Hospital, Cincinnati 29.

Society News.—Mr. William Kloepfer Jr. was appointed director of public information for the **Pharmaceutical Manufacturers Association,** with headquarters in Washington, D. C., effective Nov. 13.—Dr. Isidore S. Ravdin, Philadelphia, was named president-elect of the **American College of Surgeons** at the annual meeting of fellows Oct. 2, succeeding Dr. Owen H. Wangensteen, Minneapolis, who became president. Dr. Charles C. Higgins, Cleveland, was chosen first vice-president-elect; Dr. Allen M. Boyden, Portland, second vice-president-elect; and Dr. William E. Adams,

Chicago, was elected secretary of the college.—The officers of the **American College of Preventive Medicine** are: president, Dr. James H. Sterner, Rochester, N. Y.; president-elect, Dr. John D. Porterfield III, Washington, D. C.; vice-president for public health, Dr. Roy L. Cleere, Denver; vice-president for aviation medicine, Dr. Theodore C. Bedwell Jr., Omaha; vice-president for occupational medicine, Dr. Melvin N. Newquist, New York City; and secretary-treasurer, Dr. John J. Wright, P. O. Box 1267, Chapel Hill, N. C.—The **Central Society for Clinical Research** elected the following officers for the society for 1960: president, Dr. John H. Dingle, Cleveland; vice-president, Dr. Gordon Meiklejohn, Denver; and secretary-treasurer, Dr. Austin S. Weisberger, Cleveland.

FOREIGN

Congress of Endocrinology in Copenhagen.—The first International Congress of Endocrinology will be held in Copenhagen from July 18-23, 1960. The program will consist of 10 symposiums and a round-table discussion and of groups of shorter (10-minute) communicated papers. Speakers at the symposiums and the round-table discussion are investigators in the field of endocrinology, and titles and abstracts are invited. Forms for registration in the congress, along with forms for the submission of abstracts of short communications, may be obtained by writing to the Congress Secretariat, Dr. Svend G. Johnsen, Hormone Department, Statens Seruminstitut, Copenhagen S, Denmark. The final date for the submission of such abstracts is Dec. 31. The languages of the congress are English, French, German, and Spanish. Titles and abstracts of communicated papers should not be sent to the Program Committee, but the committee will review and arrange for the presentation of such papers in appropriate congress sessions.

CORRECTION

Treatment of Tuberculosis.—In the abstract entitled "Observations on the Treatment of Pulmonary Tuberculosis with Sulfoniazid" in THE JOURNAL, Oct. 31, page 1267, the dose should have been 0.5 Gm., not 50 Gm.

EXAMINATIONS AND LICENSURE

EDUCATIONAL COUNCIL FOR FOREIGN MEDICAL GRADUATES, INC.

Educational Council for Foreign Medical Graduates: Stations around the world. March 16, 1960 and Sept. 21, 1960. Exec. Director, Dr. Dean F. Smiley, 1710 Orrington Ave., Evanston, Ill.

NATIONAL BOARD OF MEDICAL EXAMINERS

National Board of Medical Examiners: Part I, Various Cities, June 21-22 and Sept. 7-8. Part II, Various Cities, April 19-20. Applications must be received at least six weeks before the date of the examination. Exec. Sec., Dr. John P. Hubbard, 133 South 36th St., Philadelphia.

BOARDS OF MEDICAL EXAMINERS

ALABAMA: *Examination.* Montgomery, June 21-23. Sec., Dr. D. G. Gill, State Office Bldg., Montgomery.

ALASKA:* On application in Anchorage or Fairbanks. Sec., Dr. W. M. Whitehead, 172 South Franklin St., Juneau.

DELAWARE: *Examination.* Dover, Jan. 12-14. *Endorsement.* Dover, Jan. 21. Sec., Dr. Joseph S. McDaniel, Professional Bldg., Dover.

GUAM: *Subject to Call.* Act. Sec., Dr. F. L. Conklin, Agana.

HAWAII: *Examination.* Honolulu, Jan. 11-12. Sec., Dr. I. L. Tilden, 1020 Kapiolani St., Honolulu.

IDAHO: *Examination* and *Reciprocity.* Boise, Jan. 11, 12, 13. Exec. Sec., Mr. Armand L. Bird, 364 Sonna Bldg., Boise.

INDIANA: *Examination.* Indianapolis, June 1960. *Reciprocity.* Indianapolis, fourth Wednesday of each month. Ex. Sec., Miss Ruth V. Kirk, 538 K. of P. Bldg., Indianapolis.

KANSAS:* *Examination and Reciprocity.* Kansas City, Jan. 15-16. Sec., Dr. F. J. Nash, New Brotherhood Bldg., Kansas City.

MASSACHUSETTS: *Examination.* Boston, Jan. 12-15. Sec., Dr. David W. Wallwork, Room 37, State House, Boston.

MINNESOTA:* *Examination.* Jackson, June 1960. *Reciprocity.* Jackson, Dec. 7, Sec., Dr. A. L. Gray, Old Capitol, Jackson.

NEBRASKA:* *Examination.* Omaha, June 13-15, 1960. Dir., Bureau of Examining Boards, Room 1009, State Capitol Bldg., Lincoln 9.

NEW JERSEY: *Examination.* Jan. 19-22. *Reciprocity.* Monthly, Admin. Sec., Michael E. H. Sweeney, 28 West State St., Trenton.

NORTH DAKOTA: *Examination.* Grand Forks, Jan. 6-8. *Reciprocity.* Grand Forks, Jan. 9. Sec., Dr. C. J. Glaspel, Box 228, Grafton.

OREGON:* *Examination.* Portland, Jan. 12-13. *Reciprocity.* Portland, Jan. 14-16. Ex. Sec., Mr. Howard J. Bobbitt, 609 Failing Bldg., Portland 4.

PENNSYLVANIA: *Examination.* Philadelphia, January. Sec., Mrs. Margaret G. Steiner, Box 911, Harrisburg.

UTAH: *Examination.* Salt Lake City, July 6-8. *Reciprocity.* Salt Lake City, Nov. 17. Director, Mr. Frank E. Lees, 324 State Office Bldg., Salt Lake City 1.

WASHINGTON:* *Examination.* Seattle, Jan. 11-13. Administrator, Professional Division, Capitol Bldg., Olympia.

WEST VIRGINIA: *Examination.* Charleston, Jan. 11-13. Sec., Dr. Newman H. Dyer, State Office Bldg., No. 3, Charleston 5.

WISCONSIN:* *Examination.* Madison, Jan. 14-16. Sec., Dr. Thomas W. Tormey, Jr., 1140 State Office Building, 1 West Wilson St., Madison.

WYOMING: *Examination and Reciprocity.* Cheyenne, Feb. 1. Sec., Dr. James W. Sampson, State Office Bldg., Cheyenne.

BOARDS OF EXAMINERS IN THE BASIC SCIENCES

WASHINGTON: *Examination.* Seattle, Jan. 6-7. Sec., Mr. Thomas A. Carter, Capitol Bldg., Olympia.

*Basic Science Certificate required.

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GOVERNMENT SERVICES

AIR FORCE

School of Aviation Medicine.—The research and educational facilities of the Aerospace Medical Center at Brooks Air Force Base, San Antonio, Texas, were opened to the press and invited dignitaries Nov. 12 to 14. Dedication ceremonies for the center's new school of aviation medicine on Nov. 14 were preceded by a private press tour of the laboratories which are searching for the secrets of sustaining human life during space flights. Sen. Lyndon B. Johnson addressed the assembled military and scientific leaders.

General Byrnes Awarded Legion of Merit.—Brig. Gen. Victor A. Byrnes, who retired on Sept. 30, was presented prior to his retirement with the Legion of Merit by Major Gen. Oliver K. Niess, the surgeon general. He received the award for his outstanding professional ability and his vision and leadership in his role as director of professional services in the office of the surgeon general.

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ARMY

Medical Officers to Train in India.—The Calcutta School of Tropical Medicine and Hygiene in India will be a training ground for Army preventive medicine specialists in an agreement recently concluded by the U. S. Army Medical Service and the school. Through this arrangement, Dr. R. N. Chaudhuri, dean of the school, will accept an Army physician as a resident observer on his staff for three months with spaces rotating among Army internists, preventive medicine officers, and occasionally other clinical specialists. Thus each year four officers may participate in this program. They will study such major communicable diseases as plague, cholera, dysentery, and smallpox—diseases which are rarely seen in the United States.

At present, medical officers receive similar training through tropical medicine fellowships offered by the Louisiana State University. In this program, four officers study tropical diseases in Central America each year. Major Jerome H. Greenberg, M. C., a preventive medicine officer in the Army surgeon general's office, will be the first participant in the program at the Calcutta School of Tropical Medicine and Hygiene. He will be there from early November, 1959, to February, 1960.

Medically Important Mosquitoes.—Richard R. Foote and David R. Cook of the Department of Agriculture have prepared a handbook entitled "Mosquitoes of Medical Importance," which should enable military and civilian entomologists to identify mosquitoes in any part of the world. It will serve as an invaluable aid in the prevention and control of mosquito-borne diseases that now are a scourge of many tropical countries. The Army medical service requested and supported this project because of a lack of suitable guides for entomologists during World War II, when mosquito-borne diseases were a major military problem, particularly in the Pacific areas. A unique feature of the book is a series of more than 60 pictorial keys, which will be of aid to persons having a minimum of training in identifying mosquitoes. Published as Agriculture Handbook no. 152, this book may be obtained without charge from the Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, Washington 25, D. C.

Personal.—Dr. Myles Maxfield, formerly with the medical department of the Brookhaven National Laboratories, Upton, N. Y., was appointed chief of the physical science division at Fort Detrick, Md.—Col. Adam J. Rapalski, M. C., was appointed commanding officer, U. S. Army Environmental Health Laboratory at the Army Chemical Center, Md. He replaces Col. Edward J. Dehne, M. C., who has been assigned as preventive medicine officer, headquarters, Second U. S. Army, Ft. Meade, Md.

NAVY

Three-Hundred-Foot Rise from Submarine.—On Oct. 1 two men surfaced from a depth of 300 ft. They were Commander George F. Bond, M. C., U. S. N., officer in charge of the Naval Medical Research Laboratory, and chief engineman C. G. Tuckfield, instructor at the New London Submarine Escape Training Tank. This event demonstrated that it is feasible for submarines to escape from great depths with the new "blow and go" method of submarine escape. The unique feature of this method is that the escapee does not wear any type of breathing appliance. He wears a life jacket, which carries him to the surface. The sequence of events in making the escape are as follows: The men who are to escape enter the submarine escape lock and close the doors. Water is admitted into this lock from the sea until the pressure within the escape lock is the same as the sea pressure. At 302 ft. this pressure would be about 135 lbs. per square inch. This has the effect of filling the escapee's lungs with highly compressed air. The escapee then inflates his life jacket with air, opens the door to the escape lock, and steps out. He then ascends to the surface—the buoyancy being provided by the life jacket—exhaling continuously as the reduced pressure expands the air in his lungs. During the escape 25 seconds were required to pressurize the escape lock. The ascent required 53 seconds.

New Training Program.—The Naval Medical Research Unit no. 2 at Taipei, Formosa, has organized a training program to provide opportunities for scientists in foreign countries to use the equipment at their laboratory to carry on research in virology, parasitology, clinical investigation, and entomology. Provisions have been made for at least 12 research fellows from several countries in the Far East to study under the program.

Personal.—Rear Adm. Cecil L. Andrews was appointed assistant chief of the bureau of medicine and surgery for personnel and professional operations.——Capt. Merrill H. Goodwin was named assistant chief of the bureau of medicine and surgery for Aviation Medicine and director of the Aviation Medicine Operations Division after the retirement of Capt. Oran W. Chenault in September.——Capt. C. F. Gell, M. C., special assistant for medical and allied sciences, was elected chairman of the subcommittee on acceleration and bioassay techniques for human centrifuges at the recent meetings of the aeromedical panel of NATO's advisory group for aeronautical research and development. The subcommittee will study problems of international standardization of nomenclature and bioassay end-points for centrifuges.——Capt. Oran W. Chenault, assistant chief of the bureau of medicine and surgery for aviation medicine for the past two years, retired in September after 29 years of service.

PUBLIC HEALTH SERVICE

Cancer Control Program.—The Public Health Service has created a 14-member advisory committee to its Cancer Control Program. The committee will help state and local agencies to develop services to decrease the interval between the discovery of new cancer techniques and their application. One of the duties of the new committee will be to pass on applications for $1,500,000 in federal grants for community cancer demonstration projects.

The Cancer Control Program, under the direction of Dr. Lewis C. Robbins, is in the division of special health services, Bureau of State Services. The members of the advisory committee are (1) Dr. Ulrich R. Bryner of Salt Lake City; (2) Dr. Bernard Bucove, director, Washington State Department of Health; (3) Dr. John W. Cline, associate clinical professor of surgery at Leland Stanford University; (4) Dr. Warren H. Cole, professor of surgery at the University of Illinois College of Medicine; (5) Dr. Joseph A. Cunningham, professor of pathology at the University of Alabama; (6) Dr. Harold S. Diehl, deputy executive vice-president of the American Cancer Society; (7) Dr. Lloyd M. Graves, associate professor of preventive medicine at the University of Tennessee College of Medicine; (8) Dr. John P. Lindsay, Nashville, Tenn.; (9) Dr. James J. Nickson, professor of radiology at Cornell University Medical College; (10) Dr. Mack I. Shanholtz, Commissioner of Health for the State of Virginia; (11) Dr. Charles E. Smith, professor of public health at the University of California; (12) Dr. John W. Spellman, clinical professor of surgery at the Medical School of Tufts College; (13) Dr. Samuel G. Taylor III, clinical associate professor of medicine at the University of Illinois College of Medicine; and (14) Dr. David A. Wood, professor of pathology at the University of California School of Medicine.

Health Characteristics of Children.—The extent to which acute illnesses and injuries are concentrated among children is documented in a report by the Public Health Service's National Health Survey.

The report discloses that in the year ending June 30, 1958, young children suffered acute illnesses with twice the frequency of adults. The incidence rates for acute illnesses involving either restricted activity or medical attention ranged from a high of 4.0 occurrences a year for children under 5 years of age to a low of 2.0 occurrences for adults 25 and over. On the other hand, adults over 25 averaged almost twice as many days of restricted activity from illness or injury as persons under 25. For different age groups under 25, the days of restricted activity per person per year ranged from 13.2 to 16.4, as compared with 24.1 days for adults over 25.

Home accidents among children under 15 years of age were the chief cause of injuries restricting activity or requiring medical attention. They were an important cause, along with motor vehicle and work accidents, of restricted activity in the 15-to-24-year age group. The report also gives figures, for persons under 25, on impairments and limitation of activity and mobility due to chronic conditions, hospital discharges, physician visits, and dental visits. The estimates were derived from interviews conducted by the U. S. Bureau of the Census with a representative sample of the civilian, noninstitutional population. The new report is entitled "Children and Youth, Selected Health Characteristics, United States, July 1957–June 1958," Public Health Service publication no. 584-C 1. Copies may be obtained from the Superintendent of Documents, Government Printing Office, Washington 25, D. C., at 35 cents each.

Personal.—Dr. Sam Silbergeld was appointed to a staff position in the research grants branch of the division of general medical sciences, National Institutes of Health. Dr. Silbergeld transferred from the National Institutes of Health division of biologics standards, where he was staff assistant to the director.

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DEATHS

Anderson, Joseph Gordon, Lake City, Fla.; Southern College of Medicine and Surgery, Atlanta, 1914; served with the U. S. Public Health Service; veteran of World War I; died in the Veterans Administration Hospital Aug. 11, aged 67.

Aronson, Emma Selkin Ⓜ New York City; Woman's Medical College of Pennsylvania, Philadelphia, 1910; fellow of the American College of Surgeons; associated with the staff of the Bronx Hospital, which presented her with a special bronze plaque "for many years of distinguished service"; member of the staff of the New York Infirmary and in 1956 recipient of its Elizabeth Blackwell Citation, for "outstanding contribution to the knowledge of medicine"; died Sept. 24, aged 72.

Arscott, William W., Rogers City, Mich.; Saginaw (Mich.) Valley Medical College, 1903; veteran of World War I; director of the Rogers City Band; honorary member on the medical staff of the Rogers City Hospital, where he died Sept. 7, aged 88.

Bare, Samuel Luther Ⓜ Westminster, Md.; University of Maryland School of Medicine, Baltimore, 1905; member of the American Academy of General Practice; vice-president of the Carroll County National Bank; associated with the Maryland General Hospital, Baltimore, where he died Sept. 26, aged 76.

Barnes, Benjamin Franklin Ⓜ Chattahoochee, Fla.; Marion–Sims College of Medicine, St. Louis, 1901; served as secretary and treasurer of the Jefferson County Medical Society; died in the Frasier–Ellis Hospital in Dothan, Ala., Sept. 11, aged 82.

Barney, Benjamin Arthur Ⓜ Hornell, N. Y.; Long Island College Hospital, Brooklyn, 1897; past-president of the Medical Society of the State of New York and the Steuben County Medical Society; served on the staffs of St. James Mercy and Bethesda hospitals; a director and past-president of the Maple City Cooperative Savings and Loan Association; died in the Williamsport (Md.) Sanitarium Sept. 19, aged 87.

Bates, Charles Oscar Ⓜ Greenville, S. C.; born in Spartanburg in 1886; University of Georgia Medical Department, Augusta, 1909; member of the Southeastern Surgical Congress and the Industrial Medical Association; fellow of the American International College of Surgeons and the American College of Surgeons; a member and past-president of the Southern Railway Surgeons Association; a member of the Greenville City Board of Health for many years and was serving as chairman; associated with the Greenville and St. Francis hospitals; member of the board of directors of the Peoples National Bank; died in the Greenville General Hospital Sept. 15, aged 73.

Borden, Frederic Wallace Ⓜ San Jose, Calif.; born in Spokane, Wash., Dec. 9, 1893; Stanford University School of Medicine, San Francisco, 1929; served as secretary and president of the Santa Clara County Medical Society, as president of the Visiting Nurses' Association, and on the board of directors of the local American Red Cross; from 1942 to 1947 chairman of the Procurement and Assignment Committee; invented the Borden Hemorrometer, for continuous measurement of blood loss during surgery; instrumental in the commercial development of the Stanford X-Ray Stereoscope; on the staffs of the O'Connor and San Jose hospitals; died in the Children's Hospital in San Francisco Sept. 24, aged 65.

Boswell, Brown Hill Ⓜ Robertsdale, Ala.; Tulane University School of Medicine, New Orleans, 1945; interned at the James M. Jackson Memorial Hospital in Miami, Fla., and the Touro Infirmary in New Orleans; formerly a resident at the Orange Memorial Hospital in Orlando, Fla.; died in South Baldwin Hospital, Foley, Sept. 15, aged 41.

Calder, James Ralph Ⓜ Long Beach, Calif.; McGill University Faculty of Medicine, Montreal, Que., Canada, 1947; interned at Royal Victoria Hospital in Montreal, Que., and Ste. Anne's Hospital in Ste. Anne de Bellevue, Que.; served an internship and residency at the Queen Mary Veterans Hospital in Montreal, Que.; associated with the St. Mary's Hospital where he died Aug. 18, aged 39.

Callander, Russell John Ⓜ Solana Beach, Calif.; Rush Medical College, Chicago, 1919; member of the American College of Chest Physicians; fellow of the American College of Physicians; veteran of World War II; for many years associated with the Veterans Administration Hospital in Mountain Home, Tenn.; died Sept. 12, aged 67.

Carpenter, Grant Stephen, North Sacramento, Calif.; Minneapolis College of Physicians and Surgeons, medical department of Hamline University,

Ⓜ Indicates Member of the American Medical Association.

1901; formerly assistant superintendent of the North Dakota State Hospital for Insane, Jamestown; died Sept. 15, aged 89.

Cohen, Morris, Brooklyn; Fordham University School of Medicine, New York City, 1916; first deputy medical superintendent of Kings County Hospital, where he died Sept. 25, aged 67.

Cook, Albert Edward, Caldwell, N. J.; Columbia University College of Physicians and Surgeons, New York City, 1903; died in Montclair Aug. 29, aged 81.

Craft, William Fletcher, Linton, Ind.; Indiana University School of Medicine, Indianapolis, 1915; veteran of World War I; served as health officer of Green County and of Linton; died Sept. 8, aged 73.

Curry, Claud Allen Ⓜ Terre Haute, Ind.; Indiana University School of Medicine, Indianapolis, 1920; past-president of the Vigo County Medical Society; Union Hospital staff treasurer for many years; died Sept. 20, aged 65.

Dech, Elmer Jesse Ⓜ Easton, Pa.; Eclectic Medical Institute, Cincinnati, 1894; at one time practiced in Pandora, Ohio, and served as coroner of Putnam County; died in the Easton Hospital Sept. 15, aged 88.

Dick, Edward Joseph Ⓜ Syracuse, N. Y.; Syracuse University College of Medicine, 1909; on the staff of the Crouse–Irving Hospital; died Sept. 18, aged 72.

Dion, George J., New Bedford, Mass.; Middlesex College of Medicine and Surgery, Waltham, 1930; also a pharmacist; died in St. Luke's Hospital Sept. 11, aged 68.

Dorger, Philip Henry, Covington, Ky.; Medical College of Ohio, Cincinnati, 1909; veteran of World War I; for many years on the staff of the St. Elizabeth Hospital; died Sept. 18, aged 74.

Everett, Eugene Ellsworth Ⓜ Port Charlotte, Fla.; Harvard Medical School, Boston, 1899; died in the Lee Memorial Hospital, Fort Myers, Aug. 27, aged 98.

Fischer, Edward Frederick Ⓜ Alton, Ill.; Barnes Medical College, St. Louis, 1910; on the staffs of St. Joseph's Hospital and the Alton Memorial Hospital, where he died Sept. 22, aged 77.

Flinn, James Edgar, Pittsburgh; Cleveland Homeopathic Medical College, 1904; veteran of World War I; on the staff of the Shadyside Hospital; died Sept. 16, aged 79.

Formusa, Anthony Carl Ⓜ Melrose Park, Ill.; University of Illinois College of Medicine, Chicago, 1915; died in St. Mary Mercy Hospital, Gary, Ind., Sept. 29, aged 66.

Gardner, Carol Elissa Ⓜ Montgomery, Ala.; Columbia University College of Physicians and Surgeons, New York City, 1942; interned at the Charity Hospital in New Orleans and the Harper Hospital in Detroit; served a residency at the Herman Kiefer Hospital in Detroit; for many years chief radiologist for the Veterans Administration regional office of Alabama; died Sept. 15, aged 41.

Geib, Henry Albert Ⓜ Milford, Conn.; University and Bellevue Hospital Medical College, New York City, 1914; at one time associated with the New York State Board of Health; died in Hartford Sept. 12, aged 75.

Gramling, James Walter, Gadsden, Ala.; Medical College of Alabama, Mobile, 1901; associated with the Baptist Memorial Hospital; died Sept. 6, aged 81.

Grubb, Andrew Bayne, Cripple Creek, Va.; University College of Medicine, Richmond, 1909; died Sept. 21, aged 73.

Haskell, Henry Alfonso Ⓜ Philadelphia; Howard University College of Medicine, Washington, D. C., 1929; died Sept. 28, aged 57.

Haynes, Frederick Eugene, Minneapolis; University of Minnesota College of Medicine and Surgery, Minneapolis, 1899; veteran of World War I; for many years associated with the city health department; died Sept. 16, aged 83.

Horton, Ralph Ⓜ Oneonta, N. Y.; born in Jane, Mo., Jan. 13, 1901; University of Kansas School of Medicine, Kansas City, Kan., 1926; specialist certified by the American Board of Preventive Medicine; past-president of the Otsego County Society; fellow of the American College of Chest Physicians and the American College of Physicians; member of the American Trudeau Society and the American Public Health Association; in 1946 appointed general director of the tuberculosis hospitals of the New York State Department of Health and in 1932 to its division of tuberculosis; at one time associated with the U. S. Public Health Service; associate in medicine at the Albany (N. Y.) Medical College; medical director of the Homer Folks Tuberculosis Hospital; consultant, Aurelia Osborn Fox Memorial Hospital; in 1931-1932, member of the medical staff, Loomis Sanatorium in Liberty; died Sept. 17, aged 58.

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Josewich, Alexander Ⓜ Minneapolis; University of Minnesota Medical School, Minneapolis, 1914; member of the American Trudeau Society; for many years associated with the Veterans Administration; formerly chief of the tuberculosis service, Veterans Administration Hospital; veteran of World War I; died Sept. 19, aged 69.

Karr, John Welch Ⓜ Jamestown, N. Y.; born in Keene, Ohio, Sept. 6, 1906; University of Rochester School of Medicine and Dentistry, 1936; specialist certified by the American Board of Radiology; member of the American Society of Clinical Pathologists and the Radiological Society of North America; served on the faculty of his alma mater and the University of Utah College of Medicine in Salt Lake City; member of the Atomic Energy Commission from 1948 to 1950; formerly associated with the Rochester (N. Y.) General Hospital, Strong Memorial and Monroe County hospitals in Rochester, N. Y.; in 1950-1951 associated with the Salt Lake City General Hospital and the Veterans Administration Hospital in Salt Lake City; on the staffs of the Westfield (N. Y.) Memorial Hospital, Woman's Christian Association Hospital, and Jamestown General Hospital; died Sept. 17, aged 53.

Keil, George William, Columbus, Ohio; Columbia University College of Physicians and Surgeons, New York City, 1912; for many years chief medical officer at the Ohio Penitentiary Hospital; died Sept. 21, aged 72.

Kenyon, John Marcus Ⓜ Richland, Ga.; University of Nashville (Tenn.) Medical Department, 1893; Vanderbilt University School of Medicine, Nashville, Tenn., 1893; died Sept. 17, aged 89.

Kornreich, Eugene Frederick Ⓜ Chagrin Falls, Ohio; Western Reserve University School of Medicine, Cleveland, 1924; died in the Veterans Administration Hospital, Cleveland, Sept. 21, aged 64.

Kruger, Rudolph Arthur Samuel Ⓜ Brockton, Mass.; Middlesex College of Medicine and Surgery, Cambridge, 1926; member of the American Academy of General Practice; from 1928 to 1932 served as city physician; died Sept. 18, aged 57.

Landes, Herbert Ellis Ⓜ Chicago; Rush Medical College, Chicago, 1922; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons; professor and chairman of the department of urology, Stritch School of Medicine of Loyola University; on the staffs of the City of Chicago Municipal Tuberculosis Sanitarium and the Mercy Hospital; died Sept. 24, aged 64.

Larkin, Ernest Waddill, Washington, N. C.; North Carolina Medical College, Charlotte, 1917; veteran of World War I; died in the Beaufort County Hospital Sept. 21, aged 70.

Lindsay, Guion Alton Ⓜ Dallas, Texas; Memphis (Tenn.) Hospital Medical College, 1902; associated with St. Paul Hospital, where he died Sept. 15, aged 79.

Losa, Lada Paul Ⓜ Homestead, Pa.; University of Pittsburgh School of Medicine, 1923; served in France during World War I; on the staff of the Homestead Hospital, where he died Sept. 14, aged 63.

McCoy, Mary Knauf Ⓜ Duluth, Minn.; University of Michigan Medical School, Ann Arbor, 1890; served on the faculty of her alma mater; died Sept. 14, aged 99.

McLeod, James Harvey, Santa Rosa, Calif.; Marion–Sims College of Medicine, St. Louis, 1896; past-president of the Sonoma County Medical Society; died Sept. 15, aged 90.

McQueeney, Andrew Michael Ⓜ Bridgeport, Conn.; born in New Haven, June 22, 1882; Yale University School of Medicine, New Haven, 1905; fellow of the International College of Surgeons and the American College of Surgeons; past-president of the Bridgeport Medical and Fairfield County Medical societies; served as member and president of the board of education; formerly member of the board of directors of the department of welfare and of the board of governors of the City Dispensary; for many years chief of the surgical staff of St. Vincent's Hospital; died Sept. 20, aged 77.

Mayer, Emil Valentine Ⓜ Highland Park, Mich.; Loyola University School of Medicine, Chicago, 1916; veteran of World War I; on the staffs of the Highland Park (Mich.) General Hospital and the Mount Carmel Mercy Hospital, where he died Sept. 16, aged 73.

Messmer, Anthony Conrad Ⓜ Ardmore, Pa.; Jefferson Medical College of Philadelphia, 1920; served as house physician for the Rosemont (Pa.) College and the Villanova (Pa.) College; associated with the Thomas M. Fitzgerald Mercy Hospital in Darby and the Bryn Mawr (Pa.) Hospital, where he died Sept. 25, aged 70.

Miller, Eugene Leo Ⓜ Newark, N. J.; Long Island College of Medicine, Brooklyn, 1937; vice-president of the New Jersey Dermatological Society; served as a flight surgeon during World War II, holding the rank of major; awarded the Air Medal in 1944 and the Distinguished Flying Cross in 1945; on the

staffs of St. James and Presbyterian hospitals, and the Martland Medical Center; died in the Memorial Hospital, New York City, Sept. 19, aged 46.

Morton, James Alexander Ⓜ Pontiac, Mich.; University of Michigan Medical School, Ann Arbor, 1942; interned at the State of Wisconsin General Hospital in Madison, Wis., where he served a residency; specialist certified by the American Board of Radiology; member of the American College of Radiology; chief of radiology department, St. Joseph's Mercy Hospital; captain in the U. S. Army Reserve from May 1953 to May 1955; died Sept. 16, aged 42.

Murphy, John Patrick, St. Louis; Washington University School of Medicine, St. Louis, 1912; died June 9, aged 70.

Needham, Frank Stewart Ⓜ Oak Park, Ill.; Dearborn Medical College, Chicago, 1905; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1908; from 1918 to 1938 health commissioner of Oak Park; for many years served on the council of the American Medical Milk Commissioners and as chairman of the ethical relations committee of the Chicago Medical Society, of which he was past-president of the Aux Plaines Branch; served as president of the Oak Park and River Forest Physicians' Club; associated with the West Suburban Hospital and the Oak Park Hospital, where he died Sept. 22, aged 82.

Neuland, William Ⓜ New York City; Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia, Germany, 1914; died aboard the SS New Amsterdam while on a trip to Europe June 29, aged 68.

Neumann, Gottfried Ⓜ New York City; Universität Leipzig Medizinische Fakultät, Saxony, Germany, 1933; specialist certified by the American Board of Obstetrics and Gynecology; fellow of the American College of Surgeons and the American Academy of Obstetrics and Gynecology; assistant clinical professor of obstetrics and gynecology, New York University College of Medicine; veteran of World War II; on the staff of the University Hospital, where he was chief of the sterility clinic, New York University-Bellevue Medical Center; on the staff of the Beth Israel Hospital, where he died Sept. 26, aged 58.

Newman, Henry Wise Ⓜ San Francisco, Stanford University School of Medicine, San Francisco, 1931; specialist certified by the American Board of Psychiatry and Neurology; member of the Harvey Cushing Society, American Neurological Association, and the American Academy of Neurology; professor of medicine at his alma mater; veteran of World War II; served on the staffs of the U. S. Naval Hospital in Oakland, Calif., and the Veterans Administration Hospital; died in Belvedere, Calif., Sept. 19, aged 52.

O'Connell, Edward Ⓜ Birmingham, Ala.; University and Bellevue Hospital Medical College, New York City, 1907; fellow of the American College of Surgeons; past-president of the Birmingham Surgical Society; for many years on the Jefferson County Board of Health; served on the staff of St. Vincent's Hospital; died Sept. 16, aged 75.

Pearson, Robert Garfield Jr., Sacramento, Calif.; University of California School of Medicine, San Francisco, 1954; interned at the University of California Hospital in San Francisco; died Sept. 18, aged 34.

Perri, Angelo Marco Ⓜ Philadelphia; Jefferson Medical College of Philadelphia, 1925; associate professor of public health and preventive medicine at the Hahnemann Medical College and Hospital of Philadelphia; for many years chief of the division of communicable diseases of the city department of health and since 1956 director of the medical center; a director of the Crime Prevention Association; member of the American Public Health Association; died at his summer home in Plymouth Meeting Sept. 18, aged 58.

Raine, Maxwell Francis, Crane, Texas; Ohio State University College of Medicine, Columbus, 1929; formerly health officer of Kanawha County, W. Va.; at one time health officer in Mason, Jackson, Putnam, and Roane counties, W. Va.; on the staff of the Crane County Memorial Hospital; died Sept. 11, aged 55.

Ransom, Matthias Lent Ⓜ Hancock, Minn.; Jefferson Medical College of Philadelphia, 1902; died in the Stevens County Memorial Hospital, Morris, Aug. 27, aged 85.

Reese, Emmett Francis Jr. Ⓜ Courtland, Va.; University College of Medicine, Richmond, 1899; member and past-chief of staff, Raiford Memorial Hospital in Franklin; member of the board of directors of the Southampton County Bank; died Sept. 26, aged 82.

Ring, Dean Merrill Ⓜ Major, U. S. Air Force, retired, Cedar Rapids, Iowa; State University of Iowa College of Medicine, Iowa City, 1951; interned at the University of Minnesota Hospitals in Minneapolis, where he served a residency; served a residency at the Veterans Administration Hospital in Nashville, Tenn.; specialist certified by the American Board of Surgery; chief of surgery at the Ladd Air Force Base in Alaska from 1956 to 1958 when

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he became chief of surgery at Chanute Air Force Base, Ill., where he died in the U. S. Air Force Hospital Sept. 17, aged 32.

Rizzolo, Edward Michael Ⓜ Belleville, N. J.; Baylor University College of Medicine, Dallas, 1925; during overseas duty in World War I, received the Croix de Guerre, French medal for bravery; associated with the Presbyterian, St. Michael's, and American Legion Tri-County Memorial hospitals in Newark; died in the East Orange (N. J.) General Hospital Sept. 21, aged 61.

Rosa, Henry Antonio Ⓜ Portsmouth, R. I.; Baltimore Medical College, 1899; served as medical examiner of the Portsmouth District; while practicing in Fall River, Mass., served on the board of health, and as chairman of the board of trustees of the Fall River General Hospital; died in the Truesdale Hospital in Fall River, Mass., Sept. 19, aged 84.

Roth, Aaron, Brooklyn; University and Bellevue Hospital Medical College, New York City, 1908; specialist certified by the American Board of Ophthalmology and the American Board of Otolaryngology; member of the American Academy of Ophthalmology and Otolaryngology; fellow of the American College of Surgeons; veteran of World Wars I and II; on the staff of the Beth El Hospital; formerly on the staffs of the Gouverneur Hospital in New York City, Brooklyn Women's Hospital, and the Brooklyn Jewish Hospital, where he died Sept. 9, aged 72.

Rowley, Howard Frederick Ⓜ Rochester, N. Y.; University of Michigan Medical School, Ann Arbor, 1920; specialist certified by the American Board of Pediatrics; past-president of the Rochester Pediatric Society; member of the American Academy of Pediatrics; on the staffs of the Strong Memorial and Rochester General hospitals; died Sept. 23, aged 64.

Schurter, Raymond Joseph, St. Louis; St. Louis University School of Medicine, 1923; since 1957 chief of communicable disease control for the St. Louis City Department of Health; served on the staffs of St. Mary's Hospital in East St. Louis, and St. Anthony's Hospital and St. Mary's Infirmary; died Sept. 23, aged 62.

Seabolt, Gertrude Clowes, Pasadena, Calif.; University of Southern California College of Medicine, Los Angeles, 1907; for many years school physician; died Sept. 15, aged 78.

Shaw, Alexandre, Flushing, N. Y.; University of Tomsk Faculty of Medicine, Siberia, Russia, 1923; died in the Kew Gardens (N. Y.) General Hospital Sept. 20, aged 63.

Sneed, John William, Nashville, Tenn.; University of Nashville Medical Department, 1901; died Sept. 16, aged 82.

Steinbach, Simon, St. Petersburg Beach, Fla.; Universitatea din Bucuresti Facultatea de Medicina, Rumania, 1901; for many years practiced in New York City; died Sept. 16, aged 84.

Talley, Oran Hubbell Ⓜ Corpus Christi, Texas; University of Texas School of Medicine, Galveston, 1911; veteran of World War I; since 1939 physician for American Smelting and Refining Company; died Sept. 11, aged 74.

Tessier, Claude Edward, Augusta, Ga.; Medical College of Georgia, Augusta, 1932; interned and served a residency at the Wilhenford Hospital for Women and Children and the University Hospital, where he was a member of the staff, and where he died Sept. 12, aged 54.

Van Dyke, Joseph Smith Ⓜ Palisades Park, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1903; for 25 years school physician; for many years on the staff of the Englewood (N. J.) Hospital, where he died Sept. 9, aged 84.

Van Tine, Edward Postlethwaite Ⓜ Wynnewood, Pa.; Hahnemann Medical College and Hospital, Philadelphia, 1928; specialist certified by the American Board of Anesthesiology; member of the American Society of Anesthesiologists, Inc.; assistant professor of anesthesiology at his alma mater; chief of anesthesiology at Delaware County Hospital in Drexel Hill; died Sept. 12, aged 56.

Vetter, James Harry Ⓜ Rockford, Ill.; Rush Medical College, Chicago, 1916; served in France during World War I; member of the honorary staff, Rockford Memorial Hospital; died in the Rockford Municipal Tuberculosis Sanitarium, Sept. 3, aged 69.

Wagner, Robert Lowell Ⓜ Captain, U. S. Navy, La Jolla, Calif.; born in San Bernardino Jan. 6, 1908; McGill University Faculty of Medicine, Montreal, Que., Canada, 1935; interned at the San Francisco Hospital in San Francisco; served a residency at the Lane and Stanford University hospitals in San Francisco; formerly a fellow in psychiatry at Neuro-Psychiatric Institute of the Hartford Retreat in Hartford, Conn.; veteran of World War II; specialist certified by the American Board of Psychiatry and Neurology; head of the neuropsychiatric service at the U. S. Naval Hospital in San Diego, where he died Sept. 7, aged 51.

Weigen, Anders John Ⓜ Chicago; Rush Medical College, Chicago, 1914; member of the American Academy of Pediatrics; trustee of the Chicago Medical Society and past-president of the North Shore Branch; veteran of World War I; member of

the staffs of the Children's Memorial Hospital, Augustana Hospital, and the Swedish Covenant Hospital, where he died Sept. 27, aged 70.

Weiser, Frank Andrew, Detroit; Detroit College of Medicine and Surgery, 1920; served on the faculty of Wayne University College of Medicine; formerly editor-in-chief of the *Detroit Medical News;* associated with the Receiving Hospital of the City of Detroit and the Wayne County General Hospital and Infirmary, Eloise; on the staff of the Grace Hospital, where he died Sept. 9, aged 64.

Wilcox, James Whedon Ⓜ Bay City, Mich.; Detroit College of Medicine and Surgery, 1932; member of the American Academy of General Practice; past-president of the Bay County Medical Society; chairman of the airport advisory committee of the James Clements Airport; on the staffs of the General and Mercy hospitals; died in Ranger Lake, Ont., Canada, Sept. 5, aged 52.

Wilkins, Josiah S., Hot Springs National Park, Ark.; Memphis (Tenn.) Hospital Medical College, 1913; on the staffs of the Leo N. Levi Memorial Hospital, Quachita General Hospital, and St. Joseph's Hospital, where he died Sept. 15, aged 81.

Williams, Albert Evan, Fountain City, Wis.; Milwaukee Medical College, 1908; veteran of World War I; on the staffs of St. Joseph's Hospital in Arcadia and City Hospital, Menomonie; died Sept. 10, aged 78.

Williams, Russel Hill Ⓜ Fort Lauderdale, Fla.; Ohio State University College of Medicine, Columbus, 1925; for many years head of the student health service, Denison University in Granville, Ohio; died Sept. 14, aged 67.

Williams, Warren Henry Ⓜ Manlius, N. Y.; born in Utica, N. Y., Sept. 24, 1922; Cornell University Medical College, New York City, 1948; certified by the National Board of Medical Examiners; specialist certified by the American Board of Radiology; interned at the Milwaukee County Hospital in Milwaukee and the Syracuse Memorial Hospital in Syracuse; served a residency at the Syracuse University Medical Center in Syracuse, N. Y., and the University of Texas M. D. Anderson Hospital and Tumor Institute in Houston; on the faculty of the State University of New York Upstate Medical Center in Syracuse; captain in the Army Medical Corps from 1952 to 1954; on the staff of the Crouse–Irving Hospital in Syracuse, where he died Sept. 15, aged 36.

Wilson, Richard H. Ⓜ Martins Ferry, Ohio; Barnes Medical College, St. Louis, 1898; fellow of the International College of Surgeons and the American College of Surgeons; a director of the Fidelity Savings and Loan Company; served as vice-president and director of the Peoples Savings Bank; associated with the City Hospital in Bellaire and the Barnesville (Ohio) Hospital; founder and chief surgeon of the Martins Ferry Hospital, where he died Sept. 11, aged 85.

Woods, Thomson Butler, South Norfolk, Va.; University of Maryland School of Medicine, Baltimore, 1913; veteran of World War I; died in Norfolk Sept. 4, aged 70.

Zinkhan, Paul Hudson, Ravenna, Ohio; Georgetown University School of Medicine, Washington, D. C., 1912; veteran of World War I; for many years served on the board of education; in 1949 honored by the Ravenna Junior Chamber of Commerce, which presented him its outstanding citizen's award for his work on behalf of the community; past-president of the Portage County Medical Society; on the staff of the Robinson Memorial Hospital; died Sept. 4, aged 74.

Zilboorg, Gregory Ⓜ New York City; born in Kiev, Russia, Dec. 25, 1890; University of Helsingfors, Russia, 1917; Columbia University College of Physicians and Surgeons, New York City, 1926; served in the medical corps of the Russian Army; participated in the first revolution in Petrograd in 1917 when he was secretary to the Ministry of Labor in Cabinets of Lvov and Kerensky; forced to leave Russia and came to the United States in 1919; clinical professor of psychiatry at the State University of New York College of Medicine at New York City, Brooklyn, and New York Medical College, Flower and Fifth Avenue Hospitals; visiting professor of psychiatry at Fordham University; on the faculty of Woodstock (Md.) College, and the mental health institute at St. John's University in Collegeville, Minn.; specialist certified by the American Board of Psychiatry and Neurology, Inc.; member of the American Psychoanalytic Association and the Association for Research in Nervous and Mental Diseases; in 1953 received the Isaac Ray Award of the American Psychiatric Association, of which he was a member and an academic lecturer; president of the scientific commission of the International Criminology Society; secretary and director of research, Committee for the Study of Suicide; chairman of the Consulting Delegation on Criminology to United Nations; vice-president of the third International Congress on Criminology in London; last February was the second speaker in a lecture series sponsored by the Boston University Law–Medicine Research Institute; associate visiting psychiatrist, Kings County Hospital and consulting psychiatrist at St. Vincent's Hospital; author of four books in his field; died in the Lenox Hill Hospital Sept. 17, aged 68.

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FOREIGN LETTERS

GERMANY

Metabolism After Total Pancreatectomy.—E. Kühnlein (*München. med. Wchnschr.* **101**:1592, 1959) stated that the few cases of long survival after total pancreatectomy in human beings have demonstrated that it was possible to substitute for, and balance, the secretory losses after the loss of the gland. The amount of insulin required after total pancreatectomy was strikingly low and ranged in long-surviving patients from 30 to 40 units a day. Only in those with complications, febrile affections, or insulin resistance due to development of antibodies against insulin were larger doses required. The lasting sensitivity of these patients to insulin was pronounced. This was mainly due to the great loss of glucagon-producing cells.

As far as the exocrine function of the pancreas was concerned, difficulties were mainly encountered with regard to fat metabolism and to a lesser degree to that of proteins. Individual patients varied widely as to the severity of their digestive insufficiency. Further difficulties (osteoporosis) may be incurred by increased loss of calcium and manifestations of vitamin deficiency. The danger of fatty changes in the liver, however, is relatively small. Only one case of diabetic retinopathy after total pancreatectomy has been reported. Whether the frequency of vascular damages corresponds to that of spontaneous diabetes cannot yet be decided. Derivatives of sulfonylurea are ineffective in diabetic patients after pancreatectomy, but biguanids seem effective. A patient who has undergone a total pancreatectomy requires continuous careful medical supervision, but in general his life is endurable and worth living.

Cardiac Surgery.—Successful operation for ventricular aneurysm or diverticulum in three children was reported by Derra and Loogen of Düsseldorf (*Deutsche med. Wchnschr.* **84**:1585, 1959). A 9-year-old boy was operated on in 1952. The left ventricular aneurysm was not resected, but the myocardial defect was closed with a pursestring suture placed in the superficial myocardial layers, and the aneurysmal wall was sutured over it. In the other two patients (an 8-year-old boy and 17-year-old boy) the aneurysm was resected and the myocardial defect closed with multilayered sutures during circulatory arrest under hypothermia. In the older boy the aneurysm of the right ventricle had developed after a previous transventricular pulmonary valvotomy for pulmonary stenosis. The pulmonary valve was opened during one period of circulatory arrest and the aneurysm was resected during a second. Radiologic examinations postoperatively, including angiocardiography, showed some myocardial bulging in the first patient but normal ventricular movements in the other two. The previously high operative mortality should be markedly reduced as a result of the introduction of hypothermia and the heart-lung machine. Resection or extirpation of the aneurysm or diverticulum with well-placed, multilayered sutures through the myocardium is considered the method of choice. In certain patients plastic ventricular repair may be indicated.

Hereditary Cortisone Deficiency.—H. G. Fassbender of Mainz (*Deutsche med. Wchnschr.* **84**:1595, 1959) observed two brothers who had cortisone deficiency. One died at 7 years of age and an autopsy showed the classic picture of precocious pseudopuberty as part of the adrenogenital syndrome with hypertension due to bilateral adrenal cortical hyperplasia. Their father, who died at 47 years of age and was also examined post mortem, had severe hypertensive renal and vascular lesions, a hypopotassemic myocardium, renal tubular changes, and—like his sons—cutaneous hyperpigmentation. It was assumed that father and sons had a similar, gene-determined cortisone deficiency. In the two boys the disordered steroid formation led predominantly to the production of androgens and less so of mineralocorticoids, while in the father the reverse condition existed.

INDIA

Preeclampsia.—Menon and Ramanamma (*J. Indian M. A.*, vol. 33, Sept. 16, 1959) used Veratenshun (a combination of protoveratrine with reserpine and other alkaloids of Rauwolfia) to treat 140 patients with preeclampsia. The preparation for intravenous injection contained 0.15 mg. of protoveratrine, 2.5 mg. of reserpine, and 4 mg. of Rauwolfia alkaloids per milliliter and each tablet contained 0.2 mg. of protoveratrine, 0.15 mg. of reserpine, 3 mg. of Rauwolfia alkaloids, 15 mg. of phenobarbitol, 15 mg. of pentaerythritol tetranitrate, and 2 mg. of homatropine methyl bromide. In this series 90 patients were in the antenatal period and of these 20 had a mild toxemia with blood pressure readings of 140 to 160 mm. Hg systolic and 90 to 100 mm. Hg diastolic, slight albuminuria and edema, and mild or absent symptoms; 50 patients were in labor and in all of these the toxemia was severe.

The items in these letters are contributed by regular correspondents in the various foreign countries.

All patients were treated on admission by bed rest, sedatives, a salt-poor diet, and acetazolamide. After 48 hours Veratenshun was given in addition to the other measures being used. The patients with mild symptoms received one tablet two or three times a day, increasing by one tablet daily till the optimum dose (not more than eight tablets per day) was reached. Most of these patients were 34 to 36 weeks pregnant. Of the severe cases, 12 patients were given the tablets but responded poorly. They were therefore given 1 ml. of the preparation intravenously in 20 cc. of 20% dextrose solution and their blood pressure was recorded at short intervals. Orally given therapy was then used as supplement. If no hypotensive effect occurred after the first injection, it was repeated at intervals of 6 to 8 hours till a maximum of three in 24 hours was reached. The duration of treatment varied. In 75% of the patients it ranged from 4 to 15 days; one patient received it for 70 days.

Labor was induced prematurely only if the response was poor and the patient's condition deteriorated. In the mild cases, oral therapy produced no significant benefit, the results being the same even without the use of the hypotensive drug. In severe cases, oral therapy alone was of no use but helped in maintaining hypotensive or normotensive levels after the blood pressure was brought down by intravenous injections. In 80%, the level came down in 15 minutes after injection. The maximum drop was 110 mm. Hg systolic and 70 mm. Hg diastolic. The higher the systolic pressure initially, the greater was the drop after injection. The hypotensive effect lasted 1 to 26 hours. Although the response was poor in only 11.4% of those who used the drug as compared to 40% in the controls, the drug did not help in reducing the prematurity or the perinatal death rate. No untoward effects on mother or fetus were attributable to the Veratenshun. It was thus found useful in controlling blood pressure rise in labor.

Liver in Malnutrition.—Sheth and Warerkar (*Indian J. Child Health*, vol. 8, September, 1959) studied 27 patients with protein malnutrition. The liver was palpable below the costal margin in 21 and edema was present in 19. The thymol turbidity, alkaline phosphatase level, and cephalin-cholesterol flocculation were determined in 25 patients. The first was altered in three patients and the second in six; the flocculation test result was positive in six. There was no correlation between the findings of the three tests. The degree of abnormality in liver function and the degree of edema did not correspond. Similarly there was no correlation between the degree of liver enlargement and liver function.

The plasma protein levels of 26 patients were estimated; 18 patients showed reversal of albumin-globulin ratio. The patient with the highest protein value (7.3 Gm.) showed such a reversal and had edema. The severity of the edema and the degree of protein deficiency did not show any correlation as patients without edema also had low protein values, with reversal of the albumin:globulin ratio. Paper electrophoresis was done in five cases and showed a fall of albumin in all, which was the least in the patients without edema. In three patients, alpha-1 and alpha-2 globulin levels were increased, one had a fall in alpha-1 and alpha-2 and another had reduction in alpha-1 and an increase in alpha-2. The beta globulin level was lowered in all and the gamma globulin level was reduced in three, normal in one, and raised in another. The fibrinogen level was raised in all. A liver biopsy was performed on 15 patients with no failure and no untoward effects. The prominent lesion was fatty infiltration. Although connective tissue was seen in some specimens, none showed cirrhotic changes.

Tuberculin Reactors.—A. K. Basu and co-workers (*Indian J. Child Health*, vol. 8, September, 1959) studied 500 children attending a pediatric clinic and selected at random to determine whether any correlation existed between tuberculin sensitivity and such factors as poverty, overcrowding, ventilation of dwelling, state of nutrition, and previous attacks of acute illness. The reading after tuberculin injection was taken on the third day and chest roentgenograms were taken of all positive reactors. Of the 500 children, 133 or 26.6% showed a positive reaction. The percentage of reactors increased with age. Thus, up to one year of age only 12.7% were positive reactors but 80% of the age group 7 to 12 fell in this category. The percentage of positive reactors varied inversely with the economic status of the family. More than half of the positive reactors lived in rooms of average ventilation but the same was true of nonreactors. Of the children living in one-or-two-room dwellings, 33 to 50% were positive reactors, but of those living in three to five-room homes only 25% were positive reactors. Most of the children in both groups came from families with four to seven members. Nourishment did not appear to have much influence on the tuberculin reaction.

More than half the reactors gave a history of acute illness (measles in 54.8%, whooping cough in 18.8%, repeated colds in 81.2%, and chronically infected tonsils in 56.4%). Of the positive reactors 10% had demonstrable primary tuberculous lesions in the lungs and 40% of the reactors had no radiological evidence of tuberculosis. Thirteen reactors gave a history of contact with tuberculous patients and 13 nonreactors also gave such a history. Only 8.3% of the positive reactors had a demonstrable primary lesion in the lung while 76 had a healed primary focus in the lung and 46 had a clear roent-

genogram of the chest. In these either the primary focus had healed completely or it was located elsewhere in the body.

Toxemias of Pregnancy.—S. Subrahmanyam (*Indian J. M. Sc.*, vol. 13, September, 1959) stated that increased urinary excretion of adrenocortical metabolites occurring in toxemias of pregnancy suggests an increased activity of the adrenal cortex resulting in fluid and electrolyte imbalance and such symptoms as edema, hypertension, increase in body weight, and proteinuria. Whether the adrenal medulla also plays some part in this condition was studied by the author by investigating 25 normal women, 25 normal pregnant women, 100 women with preeclampsia, and 7 with eclampsia. The patients with toxemias had blood pressures higher than 140 mm. Hg systolic and 90 mm. Hg diastolic, edema, and albuminuria.

After collecting a 24-hour sample of urine, half of it was used to determine the 17-ketosteroid content and the other half to estimate the catechol amines. The levarterenol excretion rates were 33.8, 36.3, and 68.3 mcg. in normal women, normal pregnant women, and women with toxemias respectively. The corresponding figures for epinephrine excretion were 5.7, 6.5, and 9.4 mg. The average excretion of levarterenol, epinephrine, and 17-ketosteroids was higher in those with toxemias than in normal women and normal pregnant women. The epinephrine excretion was more than in normal women but its percentage was lower than in the other two groups. The 17-ketosteroid excretion was slightly increased in normal pregnancy but in patients with toxemia it was almost double that found in normal women. The same was true of levarterenol excretion. Thus the activity of both the adrenal cortex and the medulla was increased in patients with toxemia. The excess of circulating levarterenol and epinephrine in these patients may have been responsible for their hypertension.

Genital Tuberculosis.—S. Bose (*J. Obst. & Gynec.*, India, vol. 10, September, 1959) reported a series of 80 women with genital tuberculosis. This involvement was tubal in 43, endometrial in 26, and cervical in 11. Cervical lesions were commonest in the age group 21 to 30 years. Of those with tubal involvement 15 had tuberculous peritonitis. Only six had pulmonary lesions associated with endometrial tuberculosis. There was no instance of urinary or skeletal involvement in the series. The lesions were mostly miliary with isolated tubercles and peritoneal nodules. Sixteen had matted tubo-ovarian masses with dense adhesions. Pyosalpinx containing caseous material and few adhesions was found in only one patient. The endometrium presented a normal appearance on gross examination in most patients. Ulcerative and proliferative cervical lesions were equally distributed and four were erroneously diagnosed carcinoma. In nine sterility was the primary complaint and others were found to have been infertile for several years. Menorrhagia or metrorrhagia was present in 34 and amenorrhea in 13. Ten had abdominal pain and 13 had distention associated with involvement of the pelvic peritoneum. Only four had low-grade fever and debility.

The usual treatment initially consisted of 1 Gm. of streptomycin and 10 Gm. of PAS daily for three months; 150 to 200 mg. of isoniazid was given daily if no appreciable improvement occurred or toxic manifestations appeared. An operation was performed only when the diagnosis was in doubt (8) or the patient did not respond to medical treatment (25). Twenty had panhysterectomy; in 9 there were extensive miliary tubercles on the peritoneum, omentum, and intestines and the abdomen was closed after peritoneal instillation of streptomycin; 2 had salpingectomy; and 2 had an amputation of the cervix. Intensive antituberculous treatment was continued during the postoperative period. There were no deaths.

SWEDEN

Child Accident Rate Reduced.—Intensified propaganda in Sweden for the safety of children has greatly reduced the number of fatal accidents among them, according to Dr. Ragnar Berfenstam who addressed the ninth International Congress of Pediatrics in Montreal, Canada. One result of the safety campaign was that the number of drownings among children in the ages between 10 and 14 years had dropped by about 50% over the past 40 years. The number of children per unit of population killed or injured by poison in Sweden is one of the lowest in the world. The safety campaign was largely organized by the country's pediatric clinics. Safety catches for windows, safe ovens, child-proof caps for bottles containing medicines or dangerous chemicals, and safe electrical outlets have been introduced. Moreover, the manufacturers of baby articles have given valuable advice on packaging. In the domestic science classes at school the girls are taught how to protect children against accidents.

Doctors Recommend Health Identity Card.—The steadily rising number of Swedes who travel by car at home and abroad and the large increase in serious traffic accidents has brought about appreciable medical problems. An international identity and health card containing basic medical data would help in solving these problems, according to Drs. Ored Arner and Matts Halldin of Stockholm. Most accidents necessitate a quick and adequate shock treatment of the injured, blood transfusion, and treatment against tetanus. A health and identity card would here be of immense value, as it would also aid in the treatment of acute cases of illness

occurring abroad. The card should contain name and address of the owner and next-of-kin, language spoken and understood, blood group, medical data such as earlier immunizing injections, treatment with hormones, and information about hypersensitiveness and whether the owner suffers from diabetes or epilepsy. To be of value abroad the card should be written in Swedish, English, French, German, Spanish, and Finnish.

Acromegaly.—Dr. C. A. Hamberger and co-workers (*Nordisk medicin*, Sept. 3, 1959) removed the pituitary gland by the transantrosphenoidal route in 10 patients with acromegaly. Good results could be claimed in seven patients with regression of the external manifestations of the disease. In the four patients in whom complete insufficiency of the gland was demonstrable, these external changes were most noticeable. These patients were given substitution treatment with cortisone and thyroid extract, supplemented in one with testosterone. Normal thyroid and adrenal functions were retained in the other patients. The severe headache from which two patients had suffered ceased, menstruation returned, and pregnancy went to term in one patient. No signs of activation were observed in follow-up periods of two months to three years. The authors stressed the fact that radiologic treatment with the dosage hitherto given has seldom or never achieved any essential regression of the disease.

Future of Mental Welfare.—In 1955 the Swedish Medical Association and the Swedish Psychiatric Society urged the government to explore the means by which mental welfare of the country could be adequately provided. The opinions of various scientific bodies were presented in *Svenska läkartidningen* (Sept. 25). Its authors confessed to a certain bewilderment over having to draw up housing plans in the distant future for psychiatric patients at a time when psychiatric practices are changing so fast. To what extent, they asked, will modern treatment be more effective in a closed institution than in the patient's home? They answered this question by remarking that it has become more and more desirable to treat the patient while he is engaged in normal work and lives in home surroundings. The organization of health work in industry has also promoted extramural, rather than intramural, care of the mental patient. A grave risk is often run when a patient is taken from a normal environment to the regimented atmosphere of a hospital. There must always be a residue of incurable, chronic mental patients who require hospital treatment, but even among those with senile psychosis some are amenable to modern treatment. Psychiatric hospital planning comes thus to be largely guesswork, and it is suggested that the mental hospital of the future should be planned on the basis of five beds per thousand of the population.

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in the ratio of 86:14 in the male twin and 1:99 in the female twin. The twins generously consented to submit to reciprocal skin grafting. A full thickness skin graft 1 cm. square was removed from the volar aspect of the wrist of each twin under local anesthesia, and the grafts were interchanged at the site of removal.

The grafts took well and have now persisted in each twin for two years. The graft on the male twin behaved macroscopically like an autograft. That on the female twin was deeper in color than her normal skin and retained the coarser pattern of surface markings characteristic of male skin. The graft on the male twin was microscopically normal skin which was unmistakably male on nuclear sexing. That on the female twin was also microscopically normal. In nuclear sexing the tissue at the end of the biopsy specimen was female, while that in the center was male. Blood grouping showed that the twins at this time were still blood chimeras.

The findings suggested that the female twin was completely tolerant of her brother's skin. Nuclear sexing showed that in the male this was not so, nearly all the cells of the grafts having been replaced by cells of host origin. This, however, does not imply that the graft was immunologically unacceptable, as even autologous bone grafts may be replaced. This experiment is of interest because hitherto it has not been possible to induce tolerance to homologous tissue in man.

Acrylic Resins for Intracranial Aneurysms.—The treatment of intracranial aneurysms by investing them with acrylic resin was described by Dutton, who followed up 17 patients treated in this way (*Brit. M. J.* 2:597, 1959). Initially acrylic resin implants and vessel investments were made in the brains of goats to study the immediate and delayed vascular and cellular effects. Although a mild microglial and astrocytic reaction was produced in the molecular layer of the cortex, there was no evidence of damage to the nerve cells or to the vessels. Difficulty arose in sterilization as acrylic resin cannot be boiled or autoclaved. It was therefore sterilized by exposure to 2 to 3 million rads from the cobalt bomb. This did not affect the polymerization of the powdered polymer resin. The monomer, which when mixed with the polymer solidifies, was sterilized by Seitz filtration. The polymer and monomer were mixed in empty dental anesthetic cartridges, and after standing until the right consistency was reached the cartridge was put in a syringe and the viscous resin extruded through a cannula. The resin was allowed to flow around the cerebral vessel and sac, forming a collar which was molded to the required shape.

Only those aneurysms were so treated that were technically difficult to ligate or clip. Hence in three years only 17 patients with subarachnoid hemorrhage due to aneurysms were found to be suitable for acrylic investment. Nine of these had aneurysms of the anterior communicating artery and eight had aneurysms of the middle cerebral artery. The latter group did uniformly well, with no deaths. There were four deaths in the former group. At autopsy the aneurysmal sacs were satisfactorily invested by the acrylic resin, and no bleeding had occurred at the site of the aneurysm.

Breast Feeding.—In his annual report for 1958, Prof. A. B. Semple, health officer for Liverpool, described a survey on breast feeding conducted for a period of eight months, during which 7,272 mothers with babies six weeks of age were questioned. The proportion of breast-fed infants was the same (about 25%) regardless of whether the confinement took place in the hospital or in the home. Of 3,963 mothers with normal breast development and an adequate milk supply 52% asked the doctor or the clinic to suppress lactation. Of these 25% obtained tablets for this purpose from the hospital and 70% obtained the tablets from their general practitioners. About 4% obtained such tablets from pharmacists.

Breast abscesses accounted for about 6% of cases in which lactation was suppressed. In spite of the known danger of the spread of infection in hospitals, the incidence of sepsis in infants born in hospitals was about the same as that in infants born at home—10.6% and 10.1% respectively. Breast abscess and sepsis in the infant showed a close correlation. Some evidence of sepsis was present in 23.4% of the babies of mothers who had been delivered in the hospital. The sepsis figure for babies born at home was 71.7%. The incidence of sepsis was nearly 10% in the babies of mothers with normal breasts who had been delivered in the hospital and just over 9% in the babies of mothers delivered at home.

Society for Social Medicine.—At the third annual meeting of the Society for Social Medicine held in Dundee Prof. Alex Mair described the hazards of jute manufacture, which is the major industry of the town. It has long been known in Dundee that workers in the jute industry suffer from chronic respiratory disease, but no specific pneumoconiosis syndrome, such as that occurring in cotton workers, has ever been described. Careful examination revealed that flax workers suffer from a byssinosis-like condition due to inhaled dust.

Dr. L. R. Lowe gave some interesting facts on absenteeism and works injuries in relation to smoking habits. The incidence of works injuries declines with age but increases with the amount of tobacco smoked, provided the influence of the association of age with smoking habits is eliminated by standardization. The mean number of days absent for illness increased both with age and with the amount smoked. A relation was established between the amount smoked and the incidence of works in-

juries, and this was more apparent in the younger workers. The association of smoking with absence for medical reasons was more apparent in the older group. Dr. Lowe attributed the latter to respiratory illness caused by, or exacerbated by, smoking in older persons.

Dr. R. Acheson and Prof. W. Jessop described the results of a study of the serum proteins in men who had spent their lives working in a large brewery. Gamma-globulin levels increased with age after 65 years. Albumin levels were significantly higher in those who ate meat twice a day than in those who ate it less often. Men who drank more than 12 pints of beer a day showed an increased beta globulin level.

Treatment of Warts by Hypnosis.—For many centuries warts have been charmed away by fortune tellers and the like. The treatment of warts by hypnotic suggestion is described in the medical literature, but its value is difficult to determine owing to the lack of controlled trials and the possibility of spontaneous recovery. Sinclair-Gieben and Chalmers (*Lancet* **2**:480, 1959) described a controlled trial on the treatment of warts by hypnosis. In a pilot study the warts of six patients disappeared within three months when treated by medium deep hypnosis; 14 patients were then treated by well-established methods of inducing hypnosis, such as relaxation, darkness, eye fixation, and repetitive commands. Once a state of hypnosis was induced it was suggested that the warts on one side of the body would disappear and that on awakening the patient would perform some specified action as described. Only patients with bilateral and multiple common warts of at least six months' duration were admitted to the trial, and only one side of the body was treated. This was always the side with the larger warts. Ten patients reached an adequate depth of hypnosis and four did not.

The time taken for cure on the treated side was between five weeks and three months. In the four patients whose hypnosis was only slight no benefit was obtained. If the original 6 patients are included 16 of 20 consecutive patients could be hypnotized to an adequate depth. The matched controls showed that the cure of warts can be effected by hypnosis. Improvement was always on the treated side, but the hypnosis must reach a certain depth. Those who lost their warts all showed posthypnotic suggestion in that after awakening they had performed actions suggested to them. In those who got no benefit such suggestion had failed.

Aspergillin O.—Stefanini and co-workers, who previously reported that a strain of Aspergillus oryzae (B-1273) produced a substance with a highly selective fibrinolytic activity, have obtained a purified preparation of the active material which they have tentatively named aspergillin O (*Lancet* **2**:443, 1959). The fungus was grown in the dark for five days in a liquid medium, which after filtration was passed through an anion-exchange resin (IRA-400). After adjusting the pH to 6.8 a crude precipitate of aspergillin O was obtained by adding acetone. Impurities were removed by suspending the precipitate in water and adding a solution of zinc, copper, and cadmium sulfate. Further purification was effected by dialysis against distilled water, and the solution finally lyophilized. Analysis showed that aspergillin O was largely carbohydrate in nature and contained small amounts of inorganic phosphate and nitrogen. Activity experiments showed that the purified material digested heated bovine and human fibrin in quantities as low as 0.1 Gm. Although a strong inhibitor was found in human plasma and serum, the material was effective in lysing human plasma clots, especially if added after the clot had formed. Its activity was enhanced by heparin. On incubation with plasma it showed strong anticoagulant activity. Aspergillin O was used in the control of experimental thromboembolism in dogs and in the treatment of selected cases of the condition in man.

Anthrax.—In a sampling survey of imported hides in Liverpool Semple and Hobday found that a high proportion were contaminated with Bacillus anthrax spores (*Lancet* **2**:507, 1959). The extent of contamination depended on the country of origin, the hides from Argentinian cattle showing the lowest infection rate (3%), and those from West African the highest (64%). It is likely that about 25% of the hides imported into Britain are contaminated with the spores of B. anthrax. Commercial grading of the hides does not seem to influence the infection rate. In spite of this, anthrax is rare among those who handle the hides. The survey was made in Liverpool, where only seven cases of anthrax were reported in the last five years. Normally the immunity against anthrax must therefore be high. Even so, they consider it worth while to immunize all those, such as dockers and leather process workers, who handle imported hides.

Fibrinolysis.—A new method of determining the fibrinolytic activity of whole blood was devised by Maclagan and co-workers (*Lancet* **2**:471, 1959). In an investigation of the possible role of fibrinolysis in the cause of atheroma, preliminary experiments indicated the need for a more accurate method of determining the labile fibrinolytic activity of blood. With the Maclagan technique the rate of lysis is followed by means of hourly estimations of the hemoglobin content of the clot. A graph is then plotted and the time for 50% lysis calculated. Venous blood was found to be satisfactory if collected without stasis, which produces a significant shortage of lysis time. The existence of a diurnal variation in lysis time was confirmed by a study of 53 subjects,

but this diurnal variation occurred only if they were ambulant. Subjects confined to bed showed no such variation. A significant inhibition of lysis time occurred within two hours of consuming a meal containing 1½ oz. of butter. There was a correlation between the degree of lipemia, as measured by plasma turbidity, and inhibition of lysis.

Moderate exercise greatly accelerated fibrinolysis. The effect of this was transient and disappeared within 90 minutes. It was able to overcome the inhibiting effect of large quantities of butter in the diet. The combined effects of inactivity and eating a large quantity of unsaturated fat were particularly impressive, producing about double the active control lysis times. The results were consistent with the current speculations on the effects of dietary fat in promoting, and of exercise in limiting, the development of atheroma.

Cost of Medical Care.—An investigation on national expenditure on medical care was made by J. R. Seale, who studied first hand the working of the medical services in both Britain and the United States (*Lancet* 2:555,1959). He stated that national expenditure on medical care is broadly related to the national income of the country concerned and tends to remain fairly constant in spite of economic setbacks due to recessions and wars. In the last 28 years the proportion of gross national income devoted to medical care has fluctuated between 3 and 4.5% in the United States. During the depression of the early 1930's the proportion spent was greater than it is today. It sank to about 3% in World War II.

Two conflicting groups of forces act on national expenditure on medical care. Medical, social, economic, and political sources that tend to push expenditures upward are balanced by limitation of private funds which prevents expenditure rising above a certain level. It is often thought that advances in medicine will result in the prevention of disease, a healthier population, and therefore less expenditure on medical care. While it is true that the eradication or speedy cure of many infectious diseases in the wealthier countries has occurred, this has lengthened the life span, and neoplastic and degenerative diseases have increased in consequence. These are more costly to treat. Advances in medical diagnosis and treatment have merely altered the pattern of disease. The application of new medical techniques and methods of diagnosis is increasing the cost of medical care.

As the standards of living increase more money will be spent on the hospital services. The citizens of a wealthy country expect to eat better, have more luxurious hospitals, better laboratory and diagnostic facilities, more nurses, improved operations, and better preoperative and postoperative care. Rising wages leave more money for medical care. In a modern democracy the pressures on politicians to spend public funds on medical services are strong and promises in this direction provide bait for votes in political elections, but in a nationalized health service expenditure on medical care is subservient to the demands of national defense, unemployment and old age insurance, and public utilities. A high standard of medical care provided by the state means high taxation, which is unacceptable to the public. A nation cannot have all the medical care it needs but only what it can afford or is willing to pay for. This, in practice, like expenditures for food, clothing, and housing, is a fairly constant proportion of the national income.

From a study of American statistics Seale submits the following propositions: 1. The proportion of the gross national wealth of a nation devoted to medical care tends to remain constant. 2. It rises during national economic depressions and it falls during wars, because the proportion spent on medical care is constant, and in depressions the national income falls, while during wars it becomes artificially inflated. 3. A persistent rise in real per capita gross national income will tend to result in a gradual increase in the proportion spent on health.

Parathion Poisoning.—A child was admitted to the Civil General Hospital, Singapore, with abdominal pain and vomiting. Within six hours nine more children were hospitalized for the same reason. All were seriously ill, and two died. Poisoning with an anticholinesterase was suspected and barley-water, which is a popular drink with children in this region, was finally found to be the source. More children were affected later and eight died, all from what appeared to be the same cause. The children became ill two or three hours after drinking barley-water, and rapidly became prostrate, then comatose. Excessive salivation was followed by pulmonary edema within a few hours. Large doses of atropine produced improvement. The severity of the symptoms was related to the amount of barley-water consumed, and the symptoms were worse in those who had eaten barley as well. The source of the barley was traced and it was found to be heavily contaminated with parathion, an anticholinesterase insecticide of the phosphorus type. Contamination occurred during shipment of the grain, which was stored in the same hold as the insecticide.

Cerebral Demyelinization.—Two groups of workers have drawn attention to an unusual neurological complication of disorders of the reticuloendothelial system, consisting of widespread, often confluent, foci of demyelinization in the brain, with changes in the neuroglial cells. Cavanagh and co-workers and Lloyd and Urich described patients who had Hodgkin's disease and lymphosarcoma with these neurological complications (*Lancet* 2:524-529, 1959). All patients developed an illness that progressed rapidly and without remission and finally proved

fatal. Before death clinical evidence of widespread bilateral cerebral damage was evident, dementia and pyramidal-tract lesions being the presenting symptoms in the patients with Hodgkin's disease. Homonymous hemianopia, body-image disturbance, hemianesthesia, and bulbar palsy were other notable symptoms. A patient with lymphosarcoma suffered from headaches, unilateral paresthesia, diminished vibration sense, impaired vision, and internal ear deafness.

At autopsy distinct pathological lesions were found in the brain, which were not due to infarcts from infiltration with leukemic or reticulosis deposits. The astrocytes were hyperplastic and showed gross enlargement of the nuclei, with increased affinity for stains, and mitotic figures in prophase and metaphase. It was suggested that a disturbance in normal immune mechanisms might be a factor in the production of the cerebral lesions in these patients. Another possibility is a metabolic disturbance involving lipid metabolism, particularly that of sphingomyelin.

Deaths from Poisoning.—In the last year there were 1,188 deaths from poisoning in Great Britain, 835 of them suicidal and 353 accidental. Although more men than women committed suicide, self-destruction by poisoning occurred oftener in women (456 women and 379 men). This was undoubtedly due to the larger number of women having access to aspirin and barbiturates for medical reasons. Both men and women used these drugs more than any others for suicidal purposes. Aspirin was taken by about 20% and barbiturates by just over 65% of those committing suicide by drugs. Other drugs used were mainly sleeping tablets, antihistaminics, and salicylates. The chemicals most frequently employed in suicides were cyanide, a mixed phenol preparation (Lysol), hydrochloric acid, ammonia, and nicotine in order of frequency. There were three suicides from insulin overdosage and three from taking strychnine.

The distribution of deaths from accidental poisoning by drugs and chemicals was equal among males and females. Here again the commonest causes were an overdose of barbiturates (59%) or aspirin (9%). Other substances causing accidental deaths were analgesic and soporific drugs, alcohol, and industrial solvents. Twelve children under 5 years of age died from aspirin and salicylate poisoning and four from strychnine poisoning.

Small Babies for Mothers Who Smoke.—Women who smoke have much smaller babies than do nonsmokers, according to a report in the *British Medical Journal* of Oct. 10. These findings were made in an investigation into the effect of smoking on the pregnancies of more than 2,000 women in six Birmingham hospitals. It was directed by Dr. C. R. Lowe. The infants of mothers who smoked throughout pregnancy weighed on the average 6 oz. less than those of mothers who did not smoke. This could not be attributed to sex difference or a difference between the birth weights of first and later births. Furthermore it was great enough to lower significantly the incidence of surgical induction of labor among smokers. The mean weight of infants of those who smoked 10 or more cigarettes a day was less than that of infants of women who smoked fewer than 10 cigarettes a day. Male infants of regular smokers were appreciably lighter than female infants of nonsmokers, a reversal of the usual sex difference in weight. There was no evidence that the low birth weight of infants of women who smoked was due to shortening of the period of gestation. Smoking adversely affects appetite, and it was found that smokers weighed significantly less than nonsmokers, but the difference hardly seemed sufficient to account for the difference in birth weight, since dietary deficiencies had little influence on birth weight unless they were severe.

This view was supported by the observation that when the mothers were grouped according to their weights the infants of nonsmokers were heavier than the infants of smokers for each maternal weight group. The effect of smoking was unrelated to maternal age or to the number of children a woman had had. There was nothing to suggest that cigarette smoking was related to complications of pregnancy. It was therefore concluded that smoking during pregnancy substantially retarded fetal growth. It might be that tobacco had a direct pharmacological action on the fetus, since the fetal heart rate increased when a pregnant woman smoked a cigarette. An even more credible explanation was that smoking limited the blood supply to the fetus.

Safer Surgery.—Smylie and co-workers of the Aberdeen Royal Infirmary (*British Medical Journal*, Oct. 3, 1959) reported that widespread concern about cross-infection in surgical wards has led to a more precise reevaluation of many aseptic techniques. The need for an improved surgical scrubbing became apparent during an investigation into sepsis rates in two surgical units in this hospital. Because the most troublesome of hospital pathogens, Staphylococcus aureus, is resistant to ordinary cake soap, an experiment was made with a soapless detergent cream incorporating 3% hexachlorophene, with a pH of 5.5 (that of the skin). This water-miscible anionic detergent cream, pHisoderm, contains a sulfonated ether, wool fat, cholesterols, and petrolatum, and is a surface tension reducent 40% more powerful than soap. The remarkable effectiveness of hexachlorophene as a skin disinfectant is well recognized. A detergent-disinfectant combination, pHisoHex, compares favorably with other detergents and antibacterial agents. The scrubbing time of only three minutes with it brought some criticism

from the surgical staff, but the bacteriological results showed it to be far more effective than soap in the circumstances of this trial. The amount of suds produced was a little less than with soap, and this again caused some criticism. Although a powerful disinfectant, hexachlorophene does not disinfect the skin as quickly as does 70% alcohol. Consequently the bactericidal effect of pHisoHex can be attributed to the efficient deposition of hexachlorophene as a semipermanent film on the skin of frequent users. The result, which was controlled by the use of culture mediums inhibitory to pHisoHex, showed that the new method produced a highly significant fall in the number of colonies of skin organisms grown from the finger pads of the surgical team at the end of operations.

Remuneration in the National Health Service.—With the approval of the British Medical Association, Brotherston and co-workers of the Department of Public Health and Social Medicine, University of Edinburgh, conducted an inquiry among Scottish physicians to obtain their views on alternative systems to the one in use for paying general practitioners in the National Health Service (NHS). At present the method of payment is on an annual per capita basis, which is independent of the number of patients seen or of the amount of work done by the doctor. Half the Scottish general practitioners were sent a questionnaire and nearly 80% replied. Only 2% were in favor of retaining the present system. About 12.5% thought that payment by salary was the most suitable for general application, and about 17% preferred it to be based on fees for service. Apart from 5% who suggested various combinations of these methods, about 65.5% wished to have a modified form of the present per capita system.

The doctors were asked to name the factors that should be taken into consideration in arriving at their remuneration. Very few thought that the number of patients on a doctor's list should be the only factor in determining his income, as in the present scheme. Most of them thought that the number of consultations should be taken into consideration, although they did not favor a straight fee-for-service method of computing remuneration. Another important factor mentioned was length of experience. Most thought that a general practitioner's ability and knowledge largely depends on the experience he has had and that this should be suitably rewarded. At present a newly qualified general practitioner receives the same capitation fee as his senior colleague of 20 or more years' experience.

The capitation system was generally condemned as it was thought to encourage the indiscriminate hunting for patients, or "head hunting" as it has been called, with resulting deterioration in standards of practice and undignified competition with colleagues. Payment of a fee for service was believed to involve too much clerical work (although it is done by dentists in the NHS) and to lead to overtreatment and possibly abuse. A salaried service was condemned as it would fail to relate income to ability or conscientiousness and would probably lead to loss of professional freedom.

Asked how the present system of payment could be improved, most general practitioners were in favor of reducing the maximum size of the existing list of 3,500. The alternative maximum commonly suggested was 2,500. Increased payments for maternity services, the abolition of grants for training assistants, increased supplementary payments and mileage allowances on cars, and changes in the loading system designed to discourage large lists were other recommendations mentioned.

Tolbutamide.—Loubatière's original hypothesis that the sulfonylureas lower the blood sugar level by stimulating endogenous insulin production has not been finally accepted because these drugs do not reproduce all the metabolic effects of large injections of insulin. To elucidate the mode of action of tolbutamide, Russell Fraser and co-workers estimated the plasma insulin level in normal subjects and diabetics before and after the administration of this drug. Plasma insulin activity was measured by its effect on the glucose uptake of the rat diaphragm. Tolbutamide itself neither increased the glucose uptake of the rat diaphragm used in insulin assay nor enhanced the effect of insulin. It can, therefore, be assumed that it does not lower the blood sugar level in the body by potentiating existing insulin. The blood sugar and plasma insulin activity were measured in five normal subjects and 22 diabetics before, and two and one-half hours after, giving 2 Gm. of tolbutamide. The latter were graded according to the clinical response obtained. The plasma insulin level rose in the normal subjects and in the clinically responsive diabetics but not in those who did not respond. The fall in blood sugar level correlated with this rise in plasma insulin activity. These results suggest that tolbutamide lowers the blood sugar level by stimulating endogenous insulin production, provided there is an adequate pancreatic reserve of insulin.

These authors also showed that single-dose tests of the hypoglycemic action of tolbutamide give only an approximate prediction of the long-term clinical control that is likely to be obtained. These tests can distinguish between those diabetics who do not respond and most of those who will show some persistent response, but they do not distinguish between those whose symptoms will be satisfactorily controlled and those whose response will be only fair. The difference between these good and fair responders probably depends on the adequacy of their insulin reserves. When the reserve is small, a single dose of tolbutamide may cause an impressive response, but a larger reserve is doubtless required for a sustained response to regular daily stimulation.

MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Ischaemic Electrocardiograms in Symptomless Men with a Note on the Serum Lipoproteins. D. Weitzman and E. B. Smith. Brit. M. J. 2:162-166 (Aug. 15) 1959 [London].

The authors obtained electrocardiograms from 100 hospitalized men, between the ages of 50 and 80 years, none of whom had chest pain or any evidence of cardiac disease. Abnormal tracings showing evidence of myocardial ischemia were recorded for 12 of these men. Thirty-five of the 100 patients died as a result of the illness which occasioned their admission to St. Bartholomew's Hospital in London, and autopsy was performed on 19. From 6 of the 19 patients abnormal electrocardiographic tracings suggesting myocardial ischemia had been obtained, but in all 19 the absence of any cardiac lesion, other than coronary atheroma, was confirmed by autopsy. In 12 patients, including 3 with ischemic electrocardiographic tracings, the coronary arteries were examined roentgenographically. A normal vascular pattern was observed in the roentgenograms of 6 patients from whom normal electrocardiographic tracings had been obtained. An increased anastomotic pattern, with a subendocardial plexus indicative of ischemia, was observed in the roentgenograms of the remaining 6 patients, 3 of whom had ischemic electrocardiographic tracings; in these latter 3 the anastomotic network was particularly dense. These findings emphasize the need for care in using electrocardiography in the assessment of chest pain, which is not necessarily of cardiac origin even though the tracing be abnormal.

In 59 of the 100 men, including 9 of the 12 with abnormal electrocardiographic tracings, the serum lipoproteins were examined by paper electrophoresis for the presence of an abnormal pre-beta-lipid band that is roughly equivalent to the molecular species S_f 20 to 100 undergoing flotation in the ultracentrifuge cell, as reported by Gofman and co-workers. The lipoprotein findings were compared with those in a group of 71 men with ischemic heart disease. A moderate quantity of abnormal lipid was found in a similar percentage of both groups and did not correlate with clinical coronary disease. A large pre-beta-lipid band did, however, appear to correlate with electrocardiographic evidence of myocardial ischemia.

Pulmonary Embolism and Infarction (with a Review of Cases at San Patricio V. A. Hospital). F. A. Poueymirou, E. A. R. Rodriguez and A. F. de Juan. Bol. Asoc. méd. Puerto Rico 51:259-267 (Aug.) 1959 (In English) [Santurce].

Forty cases of pulmonary embolism observed between 1947 and 1958 at the San Patricio Veterans Administration Hospital in Santurce, Puerto Rico, are reviewed. Inclusion of each case in this study was determined by one or all of the following criteria: a clinical picture with compatible electrocardiographic and/or radiologic findings; electrocardiographic pattern of acute cor pulmonale unattributable to any other condition; and the finding of either an infarcted lung area or of a pulmonary artery occlusion at autopsy. The mean age of the patients at the time the embolism occurred was 44 years; the youngest was 20, the oldest was 68. In all 40 cases the condition was traced to thrombotic embolism. In 25 patients (63%) there was evidence of significant heart disease on admission to the hospital. The condition most frequently present at the occurrence of the attacks was heart failure in 18 patients, malignant tumor in 8, fibrillation in 5, and recent myocardial infarction in 4. Fifteen of the patients in this series recovered. Autopsy findings in 25 patients indicated that pulmonary embolism had been the cause of death in 7 patients and a contributory factor in 14; in 4 it was an incidental finding.

Acute pulmonary embolism was silent in several of the patients studied. Of the 50 attacks which occurred among the 40 patients, 25 were followed electrocardiographically. In some cases the electrocardiographic tracings were not obtained immediately after the embolization, because the possibility of this diagnosis had not occurred to the physicians in charge. Only the acute cor pulmonale pattern is clearly conducive to the diagnosis of pulmonary embolism, but the complete pattern is rare and occurred in only one patient in this series. The authors emphasize that pulmonary embolism is the most frequent complication detected in hospitals. Effective means are available

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for treating and preventing this complication if the condition is recognized or suspected early. The degree of awareness of a possible pulmonary embolism must be increased in order to use effectively the diagnostic help of electrocardiography, and to interpret properly the laboratory and x-ray findings. The absence of an immediately apparent site of thrombosis does not exclude the diagnosis of pulmonary embolism. Although both surgical and medical conditions may be associated with pulmonary embolism, in the present study the number of patients under medical treatment (33) was much higher than the number of those (7) in the postoperative stage.

Chronic Cor Pulmonale Following Thromboembolism: A Clinical and Pathophysiological Study of Three Cases. L. Ehrner, T. Garlind and H. Linderholm. Acta med. scandinav. **164**:279-297 (no. 4) 1959 (In English) [Stockholm].

The authors report on 3 men, aged 43, 30, and 43 years, respectively, with chronic cor pulmonale occurring after thromboembolism of the pulmonary artery. The first of these 3 patients had signs of superficial thrombophlebitis at about 25 years of age and 4 years later probably had a pulmonary embolism. He then remained free of symptoms for 5 years, but he had repeated attacks of bronchitis, and symptoms of asthmatic type occurred. Seven years later heart failure supervened. Heart catheterization revealed pulmonary hypertension, and angiocardiography showed partial occlusion of the main branches of the pulmonary artery. The patient died, and at autopsy the clinical diagnosis of massive thromboembolism was confirmed. No sources of embolism could be found. The second patient, an athlete cyclist, was healthy until the age of 23 years when he had bilateral pleurisy and parenchymal infiltrations of unknown causation. Three years later he had a thrombosis of the right leg. After another 3 years he suddenly became dyspneic and had signs of thrombosis in the left leg. Afterwards he was completely disabled. On 2 occasions chest roentgenograms showed thin-walled cavities in the right lung associated with fever and hemoptysis. He became psychotic and died. Autopsy confirmed the clinical diagnosis of pulmonary embolism with subsequent chronic cor pulmonale. There were large organized thrombi in both branches of the pulmonary artery and a persistent foramen ovale. The third patient had symptoms of bronchial asthma at the age of 34 years. Three years later he had on 2 occasions thrombosis of the legs and an attack of unconsciousness probably due to pulmonary embolism. Soon after that he had a massive hemoptysis. On repeated occasions thereafter he had infections of a bronchopneumonic type with infiltrations into the upper lobes, in which big cavities arose. He also had chronic sinusitis. His asthmatic complaints have diminished during late years, but his dyspnea has increased, and he is at present considerably disabled.

The thromboembolic disease thus started rather suddenly in fully active, apparently healthy young men. The duration of symptoms varied between 2 and 14 years. The physiological examination revealed a low exercise tolerance; pulmonary function tests revealed normal conditions, including a fairly normal diffusing capacity of the lungs. There was an increased venous admixture in all 3 patients. In one patient at least part of the shunted blood might have passed through a persistent foramen ovale. During work the breathing rate was high at a comparatively low pulse rate. Ventilation and alveolar ventilation were excessive at rest and also during work. A considerably raised vascular resistance of the lesser circulation, resulting in a strain on the right heart, was a common finding in all 3 patients. The stroke volume was low in 2 patients at rest and decreased during work in the third. The cardiac output was low in relation to oxygen uptake in the 2 patients with the severest disease.

The diagnosis of chronic cor pulmonale after thromboembolism of the pulmonary artery should be suspected in patients with dyspnea and normal results of pulmonary function tests and no signs of primary heart disease, particularly if there is a history of peripheral thrombosis. Orthopnea seems to be a late symptom which occurs only when heart failure supervenes. Diagnosis is aided by a typical roentgen-ray picture with centrally dilated and peripherally thin pulmonary vessels, electrocardiographic signs of right ventricular strain, and a high pulmonary vascular resistance shown by heart catheterization. Angiocardiography may confirm the diagnosis.

The Ultimate Fate of Calcified Tuberculous Focus in Children and Adolescents. H. D. Renovanz. Tuberkulosearzt **13**:519-528 (Aug.) 1959 (In German) [Stuttgart, Germany].

Calcification of tuberculous foci was found in 532 of 5,216 children who underwent treatment at the Sanatorium Aprath, in the Rheinland, Germany, from 1954 to 1958. The average interval between the first radiologic manifestations of tuberculosis and radiologic evidence of calcification was 11.2 months for children under 2 years of age, and 19 to 22 months in older children. Resolution of the calcified lesions, partly by absorption and partly by softening, followed by expectoration of the caseated mass via the supplying bronchus, was observed in 1.8% of the patients. Exacerbation of the tuberculous process was observed in 13% of the children with calcified lesions. In 17% of these patients exacerbation was associated with cavitation. A comparison of these figures with those calculated

for adults shows that the risk of calcified foci becoming active and undergoing cavitation increases after puberty. The observations made in these patients indicate that a calcified focus does not invariably represent the last stage in the course of the tuberculous disease. A calcified focus often constitutes a reservoir of tubercle bacilli which may suddenly resume growth and cause reactivation of the tuberculous process.

Lymphocytic Leukemia: Symptomatology and Results of Therapy in 160 Cases. L. Heilmeyer, G. Mössner and K. Hess. Klin. Wchnschr. **37**:790-794 (Aug. 1) 1959 (In German) [Berlin].

The authors report on 125 men and 35 women with lymphocytic leukemia, who were admitted to the medical clinic of the University of Freiburg im Breisgau, Germany, between 1945 and 1957. Sixty-three (39.5%) of the 160 patients were between the ages of 50 and 60 years, 39 (24.4%) were between 60 and 70, and 33 (20.6%) were between 40 and 50. Only 2 patients were aged less than 20 years. The highest incidence of lymphocytic leukemia among those in the 5th decade is statistically significant. On admission, 93 patients (58.1%) had an increased size of the spleen, 97 (60.5%) had generalized enlargement of lymph nodes, 28 (17.5%) had localized enlargement of lymph nodes, 37 (23.1%) had enlargement of mediastinal lymph nodes, and 6 (3.7%) had enlargement of abdominal lymph nodes. Only 20 patients had a rise of temperature in the course of their disease. Sternal puncture was performed in 103 patients and confirmed the diagnosis in 91. Of 39 patients who died at the clinic, autopsy was performed in 16 and confirmed the diagnosis in all.

Of the 160 patients, 13 received roentgen irradiation alone, 53 received cytostatic chemotherapy alone, 68 received combined cytostatic chemotherapy and irradiation therapy, and 26 did not receive any specific treatment. The average survival time of the 160 patients was 3 years and 10 months. The best results were obtained in patients who received roentgenotherapy alone, with an average survival time of 4½ years. Next in order were the results obtained in patients without specific therapy, who received only cortisone and arsenics; the average survival time of these patients was 4 years and 4 months. The least satisfactory results were obtained in patients who received cytostatic chemotherapy alone and whose average survival time was 3½ years. The average survival time of patients with combined cytostatic chemotherapy and irradiation therapy was 3 years and 10 months. Other workers also reported an average survival time of 3 years and 10 months as compared with the best survival time of 4½ years observed by the authors. Triethylene melamine (TEM) was the cytostatic chemotherapeutic agent used in most of the patients. Remissions were highest among patients receiving roentgen irradiation therapy alone; next in order were remissions occurring among patients with combined chemotherapy and roentgen irradiation therapy; and the lowest incidence of remissions was observed among patients who received chemotherapy alone.

It is not easy to evaluate the reported therapeutic results, because the therapeutic subgroups of patients are too small to be considered statistically significant. Moreover, the therapeutic results depended, at least partly, on a selection of patients, in that the various methods of treatment were practiced according to the patient's general condition and the stage of the disease. In addition, it seems that the conditions inevitably leading to a certain course of lymphocytic leukemia may be inherent from the start in the individual patient and hardly subject to influence by therapy. Although cytostatic chemotherapy alone yielded the worst results, it is a valuable adjunct to treatment, because it may still be practiced with some prospect of success, while other methods, such as roentgen irradiation, would overtask the patient's remaining strength, and because chemotherapy combined with roentgen irradiation may induce a response to the latter in patients whose condition has been refractory to roentgen irradiation.

Pulmonary Disability in the Hurler Syndrome (Lipochondrodystrophy): A Study of Two Cases. J. F. Murray. New England J. Med. **261**:378-382 (Aug. 20) 1959 [Boston].

The author reports the occurrence of severe respiratory disability in a 43-year-old man and in a 3-month-old male infant with lipochondrodystrophy (Hurler's disease). The adult patient showed the classic features of lipochondrodystrophy, such as dwarfism with a grotesque physique (kyphoscoliosis), limitation of joint motion, deafness, hepatosplenomegaly, hernia, and probable cardiac involvement. The infant lacked the skeletal deformities but had corneal clouding and mental retardation. This patient died at the age of 16 months, and death resulted from acute bronchitis with bronchopneumonia. Autopsy revealed overaerated lungs with focal areas of atelectasis; Adler bodies were observed in the leukocytes, and intracellular storage of an abnormal material was found on microscopic examination. In the adult the disease became manifest in early childhood, and in the infant it was manifest at birth. Pulmonary function studies in the adult patient through a tracheostomy tube, which had been inserted for "acromegaly of the larynx" 7 years before the patient's admission to the Los Angeles Medical Center, revealed a reduced vital capacity and an increased residual volume. Obstruction of the upper airway is a characteristic feature of lipochondrodystrophy, and both patients had mouth breathing, nasal conges-

tion, and rhinorrhea. Both patients had repeated episodes of respiratory infection. Respiratory disability is one of the most important aspects of lipochondrodystrophy. Upper-airway obstruction, kyphoscoliosis, restricted chest motion, and chronic respiratory infections are common features of the disease, so that tracheostomy, which may benefit all these disabilities, should be considered early in the course of the illness.

Present-day Treatment of Hemophilia. R. Masure. Acta clin. belg. **14**:152-161 (March-April) 1959 (In French) [Brussels].

The treatment of hemophilia, which is limited at present to the prevention and cure of hemorrhage, brings up problems of local and, more especially, general hemostasis. Many direct methods of influencing blood coagulation have been tried and abandoned. Corticotherapy is the only general medicamental treatment that deserves a trial; used as an adjuvant, it may act in a nonspecific manner on capillary resistance in certain cases of subacute hemarthrosis, hematuria, or edema superimposed on hematoma, but its results are inconstant. The basic treatment for hemophilia still remains the transfusion of blood or its derivatives, because transfusion is the only method of correcting the coagulation defect by supplying the missing factor or factors. The only forms of hemophilia that need to be considered in practice are hemophilia A, hemophilia B, angiohemophilia, and hemophilia with circulating anticoagulants. Fresh whole blood, blood stored at 4 C under the usual blood bank conditions, fresh plasma kept frozen at —30 C, and irradiated and lyophilized plasma may be used in various types of hemophilia. Dried antihemophilic globulin and fresh Cohn fraction 1 are useful only in hemophilia A (classical hemophilia) or angiohemophilia (von Willebrand type). Hemophilia B (Christmas disease) responds to stored blood, standard dried plasma, or fraction PPBS, which combines prothrombin, proconvertin, antihemophilic factor B, and the Stuart factor, that is, all the factors depressed in the course of anticoagulant therapy with coumarin and its derivatives. The concentrated fractions are intended essentially for the treatment of cases refractory to the standard therapy with blood or plasma.

The amounts to be transfused to secure hemostasis will depend on the level of antihemophilic factor present in the patient's blood, on the existence or not of a refractory state (circulating anticoagulants), and on the extent of the trauma. The level of the antihemophilic factor necessary for hemostasis may have to be raised to 20, 30, or even 50% in patients who have suffered severe trauma or who are to undergo surgical procedures; consequently, the corrective power of normal plasma should always be tested by adding it to the patient's plasma in various proportions and observing the resulting recalcification and prothrombin consumption times. Antihemophilic factor A disappears from the circulation in less than 24 hours; factor B, in from 10 to 20 days. Transfusions, when needed, should therefore be given every 6 to 12 hours to patients with a deficiency of factor A and every 4 days to those lacking in factor B. Treatment with transfusions should be continued for 3 or 4 days when dental operations are to be performed, and for 8 to 10 days when the operations are more extensive. Transfusions for reasons other than severe hemorrhage and surgical operations should be avoided as much as possible in order to prevent the development of a refractory state associated with the production of circulating anticoagulants acting against the antihemophilic factors. The appearance of these inhibitors greatly aggravates the prognosis and often necessitates the administration of the concentrated fractions.

Carefully applied local treatment will usually make transfusions unnecessary, and so most of the sequelae will be prevented. Prolonged gentle pressure should be applied over wide area by means of lastex bands, or, in the case of epistaxis, by absorbable tampons of gelatin impregnated with thrombin. Punctures and injections should be avoided in patients with hemarthrosis, except when the distention of the joint is extreme. Every effort must be made to prevent trauma, however slight. Children, in particular, should be carefully watched and taught to avoid injury.

Further Experiences with Severe Allergic Reactions to Insect Stings. H. L. Mueller. New England J. Med. **261**:374-377 (Aug. 20) 1959 [Boston].

The author reports on 57 male and 27 female patients, between the ages of 3 and 56 years, who had systemic reactions to stings of bees and wasps. Of the 84 patients, 12 had slight general reactions, 36 had general reactions, 23 had severe general reactions, and 13 had shock reactions. The more rapid the onset of symptoms after the sting, the more severe the reaction was likely to be. Sixty-three (75%) of the 84 patients had a family history of allergy, and 28 of these had a personal history of other allergy as well; these 63 patients had a tendency to have more severe reactions than the 21 who had no family or personal history of other allergy. Six of the 84 patients were not treated for various personal and economic reasons. Seventy-eight patients were treated, but 2 of these did not return for treatment. Of the 76 patients with continuing treatment, 13 have completed 3 years of perennial inoculations with a mixed whole-insect extract of equal parts of bee, wasp, hornet, and yellow jacket. The starting point in dilution for treatment with this polyvalent insect extract varied from 1:100,000,000 to 1:1000. The remaining 63

patients are still receiving maintenance doses of the polyvalent insect extract. Of the 76 patients, 30 (about 40%) have had a total of 48 stings after treatment was started. With one exception, all the patients who have been stung while on a maintenance dose of 0.15 cc. or greater of a 1:100 dilution of the polyvalent insect extract, or who have been stung after completing 3 years of treatment, have had no resulting systemic symptoms.

Severe reactions to insect stings occur more commonly than is generally supposed, and it is possible that unrecognized cases account for some of the sudden deaths attributed to heart failure and heat prostration in the insect seasons. Identification of the insect causing the sting reaction is unreliable, unless the insect is captured and identified by an expert. Intracutaneous testing reveals that extreme sensitivity may occur in these patients, that multiple sensitivity is usually present, and that these tests, in general, can be used as a guide for starting doses in treatment. In all patients who have had a systemic reaction to a sting by a bee, wasp, hornet, or yellow jacket, treatment with a mixed whole-insect extract of these 4 types of insects is advised, starting with the dilution that gives the "initial positive test," and increasing gradually to a maintenance dose of 0.2 to 0.3 cc. of 1:100 dilution. If testing is not performed, it is recommended that patients be started at 0.05 cc. of a dilution of 1:100,000,000.

The Painful Reaction to Alcohol in Hodgkin's Disease. V. Giuliani and M. Talarico. Riforma med. 73:876-880 (Aug. 1) 1959 (In Italian) [Naples].

The authors report on the reaction to the alcohol test in 16 patients (11 male and 5 female ranging in age from 25 to 39 years) with malignant lymphogranuloma (Hodgkin's Disease), in 6 patients with various types of lymph node involvement, and in 5 normal individuals. The disease was in the active stage in 10 of the 16 patients with lymphogranuloma and stationary in the other 6. These latter patients had been treated with nitrogen mustard or irradiation therapy; the other 10 had received no treatment. Of the patients with lymphogranuloma, alcohol was given orally to 4, intravenously to 8, and orally and intravenously to the remaining 4. Pain developed in 3 of the 10 patients with the disease in an active stage. There were no positive results among the patients with lymph node involvement other than those in Hodgkin's disease. Therapeutic treatment, followed by a remission of the disease, had a marked effect on the results of the tests, which became negative when the disease became stabilized. Vasodilator preparations, given orally or topically, had no effect on the pain induced by the alcohol. The results of the test were not influenced by the administration of tetraethylthiuram disulfide. Differences in the way in which the alcohol was administered did not greatly affect the results; the authors, however, believe that the intravenous administration is preferable. The pain appeared immediately, especially in patients who received the alcohol intravenously, lasted for from 30 to 40 minutes, and usually passed away spontaneously. Involvement of the lymph nodes of the area in which the pain occurred was not observed, although during and after the test the nodes were more perceptible on palpation. The authors believe that the accumulation in the lymphogranulomatous tissue is not due to a local vasodilation, but to a depolymerization of the chemical constituents of the intercellular substance of the tissue, especially in the hyaline-fibrous part of the sclerotic zones which are very extended. Because of the low percentage of positive reactions, the authors believe that the test, though specific, is not pathognomonic of malignant lymphogranuloma.

Treatment of Severe Tetanus. J. R. Lawrence and M. J. W. Sando. Brit. M. J. 2:113-118 (Aug. 1) 1959 [London].

The authors report on 9 patients with severe tetanus, who were observed from June to October, 1957, at the Royal Adelaide Hospital and who were treated by the administration of doses of tubocurarine sufficient to paralyze the voluntary muscles and by artificial respiration. Each patient was first given 300,000 units of antitetanic serum, half of it intravenously. Tracheostomy was performed under general anesthesia, when it was indicated. At the same time débridement of the entry wound was performed when necessary, and a cuffed rubber tube was inserted. A "polythene" catheter was introduced to administer nourishment and drugs by intravenous drip. The earlier patients received mephenesin, and the later ones chlorpromazine. Penicillin was given, and the sedatives found to be useful were promethazine, pethidine, chlorpromazine, paraldehyde, and chloral. Sterile tracheal toilets were done when tracheostomy was performed.

Curarization was begun with artificial respiration in instances in which heavy sedation failed to inhibit spasms, especially of the muscles of respiration. Curarization was instituted by the intravenous route, but maintenance could be effectively achieved by intramuscular injections of between 60 and 90 mg. of tubocurarine. The indications for further doses were a rising blood pressure or pulse rate, the appearance of muscular twitches, movements of the tongue, face, or lips, or breathing motions. The ideal time for decurarization was when the patient could tolerate tracheal suction and could cough without developing generalized spasms. It was determined by trial. The period required varied from 18 to 72 hours, a careful watch being maintained for evidence of persistent severe tetanic activity.

Four patients died, 2 of them of pulmonary embolism and another in acute renal failure. Several other complications occurred, including hyperglycemia and bone-marrow depression, thought to be related to prolonged nitrous oxide administration. Hyperglycemia in 3 patients was so severe as to warrant the use of insulin. The authors believe that the technique of paralysis and mechanical artificial respiration has a real place in the management of tetanus. It is indicated in the fulminating case or in the severe case when sedation and other relaxant agents fail to control reflex spasms and thoracic rigidity. It should be begun as soon as it is evident that simpler measures will not adequately control the tetanic process.

Essential Hyperlipemia: Review. E. Dollerup and S. E. Jensen. Ugesk. laeger **121**:1151-1159 (July 23) 1959 (In Danish) [Copenhagen].

Of 141 cases of essential hyperlipemia published, only 112, in 17 children and 95 adults, have been described in detail. The disease appears without known causal relation with any other disease and is marked by considerable increase in the neutral fat level of the serum and by milky appearance of the serum in the fasting state. The serum cholesterol and phospholipid concentrations are often increased. While essential hyperlipemia was previously regarded as a benign disease, more recent reports of accompanying grave vascular symptoms have altered this conception. Essential cholesterolemia is distinguished from essential hyperlipemia in that the fasting serum is clear and there is no, or only moderate, increase in the serum neutral fat value. Some cases of essential hyperlipemia are asymptomatic and are recognized only through accidental observation of the lactescent serum. The clinical picture is most frequently described as a triad, consisting of (1) cutaneous xanthomas, (2) attacks of abdominal pain, and (3) hepatosplenomegaly. The cause of the disease is not known. In some cases low-fat diet seems to be effective; in other cases dietetic treatment is without special value, and heparin effects only a slight passing reduction in the serum lipids. Clinically, some cases have several symptoms in common with essential hypercholesterolemia, and a transition form may be considered. The disease occurs at all ages, is most frequent in males, and there may apparently be familial occurrence.

Toxic Megacolon in Ulcerative Colitis. J. L. A. Roth, A. Valdes-Dapena, G. N. Stein and H. L. Bockus. Gastroenterology **37**:239-255 (Sept.) 1959 [Baltimore].

The authors report on the occurrence of 15 attacks of toxic megacolon in 12 patients with ulcerative colitis, who were studied on the gastrointestinal service of the Graduate Hospital of the University of Pennsylvania, in Philadelphia, between 1943 and 1958. There were 8 men and 4 women, ranging in age from 20 to 66 years. The term "toxic megacolon" has been used to describe extreme dilatation of a segment of the colon or of the entire colon, which occurred in all these patients during a fulminating first attack of ulcerative colitis, an acute fulminating relapse of the relapsing-remitting type of the disease, or a fulminating exacerbation of the chronic, continuous course of the disease. It was noted in most patients in whom the ulcerative colitis was initially localized to the descending colon or in whom it involved the entire colon or a regional segment. No instances of toxic megacolon were observed in patients in whom the disease was initially limited to the rectum or the rectosigmoid, or in those with enterocolitis (regional stenosing enteritis, usually involving the terminal ileum, in association with ulcerative colitis).

Toxic megacolon may occur as a complication very early or very late in the course of ulcerative colitis. The colonic changes may be reversible, with the colon returning to normal caliber between recurrences of the marked dilatation. A narrowed, apparently stiffened portion of the colon may dilate to 3 or 4 times the normal caliber with a subsequent attack. The clinical configuration of toxic colon in these patients suggested almost complete colonic obstruction with impending perforation. The abdomen was rotundly protuberant, with extreme distention of the colon with gas. Although bowel sounds were usually present, the abdomen was quiescent, with infrequent and feeble peristaltic activity. The transverse colon was dilated in all the patients, and was the site of maximal dilatation in most. The average diameter of the colon during the phase of toxic dilatation was 9 cm., as revealed by the roentgenogram. Profound toxicity was a constant accompaniment, manifested by a septic spiking fever, drawn facies, tachycardia, extreme lethargy, and high degree of leukocytosis, with toxic granules and left shift to immature forms of neutrophils. Striking abnormalities of sensorium or mental behavior were noted in most of the patients; these abnormalities included anxiety, profound depression, hysterical behavior, a state resembling parkinsonism, and extreme listlessness. Severe nutritional deficits with low hemoglobin values, hypoalbuminemia, and hypoprothrombinemia were observed, but hypopotassemia was usually not present.

The complications of free perforation, thrombophlebitis, and liver disease were observed more frequently in the 12 patients in whom toxic megacolon occurred during a fulminating attack of ulcerative colitis than in a group of 10 patients with a fulminating first attack of ulcerative colitis reported on by other workers. Two of the 12 patients had fatty liver (as revealed by autopsy), and 3 had

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moderate Bromsulphalein retention. The duration of the marked colonic dilatation varied from 5 days to 2 months (average, 12.7 days). The termination of the dilatation was abrupt in 9 of the attacks—with 3 patients undergoing an emergency operation for impending perforation, with remission shortly after the institution of corticotropin therapy in 2 patients, with spontaneous remission in 3 patients, and with death in 1 patient. Dilatation of the colon subsided gradually in 6 attacks of toxic megacolon —spontaneously in 3 and after corticotropin therapy in the other 3.

Overwhelming toxemia is probably responsible for the extreme dilatation of the colon through inflammatory degenerative changes or acute necrotic destruction of the muscle fibers or myenteric plexuses, or both. Aerophagy may contribute to the pathogenesis of this dilatation as well as antecedent distal stenosis (without actual obstruction) in some patients. Therapy must be intensive and comprehensive with putting the intestines at complete rest, nothing being administered by mouth during this acute toxic phase. Treatment should include intubation and continuous suction and the administration of antibiotics, blood or protein or both, vitamins B, C, and K, electrolytes (potassium), oxygen, and possibly adrenal steroids. The need for emergency ileostomy and subtotal colectomy should be considered. Six of the 12 patients were treated only with medical measures, with 1 death; surgical intervention was required in the management of the other 6 patients, with 2 deaths, both after emergency subtotal colectomy and ileostomy.

SURGERY

Cancer of the Lung in Tuberculous Patients. N. C. Hamel, J. N. Briggs and L. G. Ludington. California Med. **91**:131-133 (Sept.) 1959 [San Francisco].

The records of 7,680 tuberculous patients admitted during a 5-year period to Olive View (Calif.) Sanatorium showed that 4,010 were over the age of 45 years, and that 54 (1.4%) of these had both cancer of the lung and tuberculosis. Not one of the patients with tuberculosis whose age was less than 45 years had this complication. The incidence of carcinoma of the lung in this series of patients with tuberculosis was estimated to be 8 to 10 times higher than that noted in a comparable segment of the general population. Careful examination of serial roentgenograms in all cases of suspected pulmonary lesions was found to increase diagnostic acuity. Scalene node biopsy, cytological studies, and bronchoscopy were of less diagnostic help. The most effective diagnostic procedure has been early thoracotomy in patients in whom there was a reasonable possibility of carcinoma. Thoracotomy was carried out in 25 of the 54 patients with tuberculosis, and diagnosis of carcinoma of the lung was made at the time of operation in 21 of the 25 patients; all except 4 of these patients were found to have tumors of an epidermoid type. Only 2 of the patients with combined disease were women.

The resection in 12 of the patients was intended to be curative in type. Curative resections were done in a greater proportion of patients with active tuberculosis than in those with inactive tuberculous disease. The authors emphasize that it is easy to overlook the slow progress of malignant disease in a patient who has residual fibronodular tuberculosis. Moreover, close and accurate follow-up is not always available in patients with inactive tuberculosis, whereas almost all patients with active disease are in the sanatorium or under close outside supervision. In 85 cases of carcinoma of the lung in nontuberculous patients observed at Olive View Sanatorium in the 5-year period here reviewed, the operability rate was 24%, as compared with 46% for the 54 patients with both tuberculosis and cancer. Curative resections were made in 12% of the nontuberculous patients with cancer, as compared with 22% in patients who had both cancer and tuberculosis.

Surgical Experiences in the Treatment of Congenital Mitral Stenosis and Mitral Insufficiency. G. W. B. Starkey. J. Thoracic Surg. **38**:336-352 (Sept.) 1959 [St. Louis].

The author presents 5 patients (3 girls and 2 boys) with congenital mitral stenosis, who were operated on at the Boston Children's Medical Center. The age range from 2½ to 15 years. The diagnosis was made on the basis of the early age of detection of a mitral diastolic murmur (between the ages of 2 weeks and 14 months in 4 patients and at 5 years in the 5th). These children were very ill and in congestive failure. Severe respiratory infections, underdevelopment, and dyspnea were present in all. Three of the 5 patients had had repeated bouts of syncope, often accompanied by cyanosis. A 4th patient had grand mal seizures, accompanied by cyanosis during crying spells. Hepatomegaly was noted in all 5 patients, splenomegaly in 3. Normal sinus rhythm, an apical diastolic rumbling murmur, loud pulmonic second sound, and P pulmonale were observed in all 5 patients. An apical systolic blowing murmur was found in 3 patients, and right ventricular hypertrophy in 4. X-ray examination showed cardiomegaly in all, with enlargement of the right ventricle, left atrium, and pulmonary artery.

Four of these patients were operated on by the "closed" method, a standard left 4th intercostal space incision being used. There was one death on the 5th postoperative day for reasons that were not clear. The results were excellent in one patient and fair to good in the other 2 survivors of the "closed" method of operation. A 5th patient was

operated on by the "open" method with aid of a pump-oxygenator. At the end of the procedure the heart began to fail and could not be resuscitated.

The author cites 2 patients with congenital mitral insufficiency who were operated on within the last year. Neither of these patients represented the commoner types of congenital mitral regurgitation, that is, a cleft mitral septal leaflet associated with an ostium primum or atrioventricular canal, or the rarer absent, or vestigial, posterolateral mitral leaflet. These 2 children, like the 5 previously described with congenital mitral stenosis, were very ill and were doing poorly on a medical program. One of them was operated on by means of an "open" method with the aid of a pump-oxygenator, followed by some improvement, and in the other a "closed" method was used, with excellent result.

These 2 congenital anomalies of the mitral valve seem to be rare, and their prognosis is unfavorable. It is suggested that this diagnosis be more seriously entertained in the future and that surgical intervention be undertaken in these seriously ill children.

Simplified Technique for Direct Vision Pulmonary Valvotomy. C. R. Lam and R. E. Taber. J. Thoracic Surg. **38**:309-318 (Sept.) 1959 [St. Louis].

If the surgeon is to make the best possible correction of pulmonic valve stenosis, he must be able to see what he is doing. This principle has been reluctantly accepted, because the transventricular method popularized about 10 years ago by Brock had many attractive features, and its immediate clinical results appeared to be satisfactory. A recent survey revealed, however, that many patients having been treated by the transventricular method required a second valvotomy by an open technique. The authors at first used open valvotomy with hypothermia, but observations on a woman who had a combination of atrial septal defect with pulmonic stenosis led them to carry out open pulmonary valvotomy without hypothermia. Since then they have used open pulmonary valvotomy without hypothermia and without the pump-oxygenator in 48 patients, with a single death which occurred in the youngest patient in the series, a child 18 months of age.

There have been no postoperative complications in the other 47 patients. In the short period of follow-up, clinical studies have indicated an excellent correction of the defect in every patient. In several cases the murmur has disappeared, and in all there has been a reduction in heart size and electrocardiographic evidence of less right ventricular hypertrophy. With the experience with the transventricular operation in mind, there may be skepticism about the long-term results. The operation is suitable only for pulmonic stenosis of the valvular type. Differentiation of this type from isolated infundibular stenosis and other congenital defects should be possible with the diagnostic techniques available.

The Etiology and Prevention of Atrial Fibrillation After Mitral Valvotomy. C. F. Kittle and J. E. Crockett. J. Thoracic Surg. **38**:353-361 (Sept.) 1959 [St. Louis].

The authors reviewed the cases of 254 patients who had undergone mitral valvotomy at the University of Kansas Medical Center in Kansas City, Kan., and the Kansas City (Mo.) Veterans Administration Hospital since 1953, giving particular attention to the occurrence of postoperative atrial fibrillation and the prevention of this arrhythmia. Ninety-nine of the 254 patients had atrial fibrillation before the operation, and 155 had a normal sinus rhythm preoperatively. Atrial fibrillation developed after operation in 41 (26%) of the 155 patients, this being the commonest complication after mitral valvotomy. Atrial fibrillation usually developed between the 2nd and the 4th day after the operation, although it began as early as the 1st and as late as the 15th day. The occurrence of the fibrillation was not related to the age of the patients.

The frequency of postoperative atrial fibrillation was significantly lower in those patients receiving both digitalis and quinidine postoperatively. It is concluded that the combined use of these drugs is beneficial in preventing this deleterious arrhythmia. Local trauma to the left atrium incident to the atriotomy is probably the most important factor in the etiology of this arrhythmia. Conversion of postoperative atrial fibrillation to sinus rhythm can usually be accomplished, while this is more difficult in those with preoperative atrial fibrillation.

Congenital Hernia or Prolapse of the Diaphragm in Children. R. M. Konrad and A. R. Fahmy. Arch. klin. Chir. **291**:253-270 (no. 3) 1959 (In German) [Berlin].

The authors feel that unfamiliarity with the symptoms and incorrect or belated diagnosis of congenital diaphragmatic defects are the chief reasons why newborn infants with such defects do not receive suitable surgical treatment, although improvements in anesthesia, in surgical techniques, and in preoperative and postoperative care during the past 2 decades justify immediate or early operation in such congenital thoracic dystopias of the abdominal organs. A knowledge of the ontogenesis of the diaphragm is essential for an understanding of the variety of its congenital defects. There are 2 main groups of organ dystopias in the chest during childhood. If the displaced abdominal organs are surrounded by a hernial sac, the dystopia is designated as a diaphragmatic hernia; in the absence of a hernial sac, the condition is re-

ferred to as a prolapse through the diaphragm. This differentiation is important not only from the anatomic but also from the clinical viewpoint.

The authors feel that all infants with congenital diaphragmatic hernia or prolapse, with the exception of those with hiatus hernia of the sliding type, who have symptoms during the first hours, days, or weeks should be subjected to surgical treatment, because such treatment is highly successful in comparison with the high mortality that results from conservative treatment. At present, in Germany, from two-thirds to three-fourths of the children with congenital deformities of the diaphragm still die within the first month of life. In some cases a correct diagnosis is never made, but the condition is designated as "dextrocardia"; in other cases valuable time is wasted with attempts at conservative treatment. The possibility of diaphragmatic defects should be taken into consideration in all infants who present with cyanosis and dyspnea.

The authors review data on 24 children with congenital diaphragmatic hernia or prolapse, who were observed at the surgical clinic in Düsseldorf during the past 8 years. All but one of these were subjected to surgical treatment. These children ranged in age from 1 day to 13 years. Of the 4 children who died (17% surgical mortality), 2 died within 4 hours. In these 2 children death was due to respiratory insufficiency, which, in turn, was caused by pulmonary hypoplasia; in one damage to the brain, caused by anoxemia during the preoperative phase, may have contributed to the fatal outcome. The third child died one month after operation of pneumonia, and the fourth 6 weeks after operation from an acute relapse. The 9 children subjected to follow-up examination were free from relapse.

Adenomatous Polyposis of the Stomach: Clinical and Anatomic Analysis of 20 Cases. G. Naldini and A. Salvini. Arch. ital. chir. **85**:303-319 (no. 4) 1959 (In Italian) [Bologna, Italy].

The authors report on 20 patients with adenomatous polyposis of the stomach, who were operated on at the Institute for Pathological Surgery of the University of Milan, during the period from 1948 to 1957; 334 patients with malignant gastric tumor were operated on at the same institute during the same period. The 20 patients were 50 to 73 years of age; 11 were female, and 9 male. A family history of polyposis was present in 3 instances. Concomitant diseases were: hypochromic anemia in 15 patients, thyroid trauma in 2, uterine fibromatosis in 2, cholecystic calculi in 2, chronic colitis in 2, and lithiasis of the kidney in 1. The antrum and the corpus of the stomach constituted the most frequent localization in 11 patients. Nine patients presented diffuse gastritis – hypertrophic in 5, athrophic in 2, and mixed in the others. Seven patients presented simple polyps, and 4 atypical polyps; 13 (65%) of the 20 patients, therefore, presented either incipient or actual malignancy. In half of the patients the polyposis was diagnosed after the patient had suffered from dyspeptic disturbances for a period of 1 to 12 years. The disturbances were always related to meals. Five patients presented early postprandial vomiting, which was followed by relief of symptoms. Malignancy was found histologically in 3 of 9 patients who on roentgenologic examination had been diagnosed as carriers of benign tumors. A typical adenoma was found histologically in each of 5 patients in whom malignancy had been suspected on roentgenography. Two simple adenomas, 1 adenoma with incipient atypia, and 3 adenomas with malignant degeneration were found histologically in the other 6 patients who on roentgenologic examination had been diagnosed as having malignant gastric neoplasia. Fourteen patients were treated by subtotal gastric resections, and 6 by polypectomy. A normal postoperative course was observed in all the patients, with the exception of one who had been subjected to gastric resection. On follow-up examination 1 to 10 years after the operation, 8 patients were found in good general condition. One patient suffered from a local relapse due to adenoma 13 months after the operation. A peritoneal carcinosis appeared 3 months after the gastric resection in a patient in whom histological examination had shown a polyp with malignant degeneration. Two patients died of unknown cause, and 8 were lost to follow-up.

The authors point out that the difficulty of an exact clinical, roentgenologic, and even operative evaluation may be overcome by means of a rapid diagnosis with frozen sections made during the course of the operation. Because of the high incidence of incipient malignancy and of forms with a highly suspicious course, the authors suggest a radical operation whenever there are no contraindications. The good results obtained with polypectomy, however, show that even this type of operation may be beneficial if it is combined with an extensive excision of the gastric mucosa around the base where the tumor is implanted.

Symptomatology and Pathophysiology of Isolated Congenital Pulmonary Stenosis. A. Tsakiris, F. Schaub and A. Bühlmann. Schweiz. med. Wchnschr. **89**:801-810 (Aug. 1) 1959 (In German) [Basel, Switzerland].

The authors report the clinical, electrocardiographic, radiologic, and hemodynamic findings in 11 male and 7 female patients, between the ages of 10 and 54 years, with isolated congenital pulmonary stenosis. Of the 18 patients, 6 had mild pulmonary stenosis, and 11 had moderate to severe pulmonary stenosis. The main symptoms of the 11

patients included reduced work capacity with exertional dyspnea, precordial pain at rest and during exertion, and tachycardia, but cyanosis was absent. The 6 patients with mild degrees of stenosis were usually asymptomatic and, in general, were able to lead a normal life without any complaints. On auscultation, the most prominent physical finding was a loud systolic murmur over the pulmonic area; it showed a "diamond shape" on the phonocardiogram and was frequently associated with splitting of the diminished second heart sound. The degree of splitting, i. e., the distance between the 2 segments of the second heart sound, is a reliable index of the severity of the stenosis. Five patients had, in addition, an atrial sound, and 7 had a systolic click. The chest roentgenograms of all 18 patients showed a prominent conus pulmonalis as a result of the poststenotic dilatation of the pulmonary arteries. Fourteen patients showed radiologic evidence of right ventricular hypertrophy. The right atrium was prominent in 13 patients, and a diminished pulmonary circulation was revealed by the chest roentgenograms of 9 patients.

The electrocardiograms of the 11 patients with more severe stenosis revealed a pronounced pattern of right ventricular hypertrophy and, in addition, impairment of the right side of the heart and an overload placed on the right atrium. Atrioventricular block was observed only once, and a right bundle-branch block twice. The pattern of right ventricular hypertrophy is of unique diagnostic significance, because it virtually never occurs in any other noncyanotic congenital heart disease. During cardiac catheterization the pressure gradient between the right ventricle and the pulmonary artery was always above 5 mm. Hg. The lowest right ventricular pressure was 35 mm. Hg, and the highest was 230 mm. Hg. The continuous recording of the pressure curve, as the catheter is drawn back from the pulmonary artery into the right ventricle, is of invaluable diagnostic aid in differentiating valvular from infundibular stenosis; of the 18 patients, 14 had valvular stenosis, 3 had infundibular stenosis, and in 1 patient the site of constriction could not be determined.

The surgical treatment of severe, isolated pulmonary stenosis was inaugurated by Brock and has become a generally recognized and routinely practiced procedure. Today the dilatation of the valvular opening or the resection in case of infundibular stenosis is being performed under direct vision on the open heart with the aid of hypothermia or a heart-lung apparatus and extracorporeal circulation respectively. The operative mortality rate, which first was relatively high for pulmonary valvulotomy and for the technically more difficult resection in case of infundibular stenosis, has been reduced from 20% to about 5% in favorable cases. The results concerning subjective complaints and general work capacity, as well as with regard to the reduction of pressure values in the right ventricle, appeared to be excellent. Patients with mild stenosis, whose work capacity has not been impaired, do not require treatment but should be carefully watched. The indications for operations should always be considered carefully in those patients who have considerable difficulties and an increased pressure in the right ventricle (limiting value: 80 to 100 mm. Hg).

The Surgical Treatment of Isolated Infundibular Stenosis. H. Swan, W. P. Hederman, P. S. Vigoda and S. G. Blount Jr. J. Thoracic Surg. 38:319-335 (Sept.) 1959 [St. Louis].

Subvalvular pulmonic stenosis with intact ventricular septum is more commonly referred to as "isolated infundibular stenosis." After citing previously published estimates on the incidence of this congenital cardiac defect, the authors present the histories of 5 patients with isolated infundibular stenosis, who were subjected to surgical treatment. Their ages ranged from 9 to 21 years. It appears that infundibular stenosis is caused by arrest of the normal involution of the bulbus cordis, which should be incorporated into the right ventricle by the end of the second month of intrauterine life, thus forming the outflow tract of the right ventricle. The stenosis may be of 2 types: 1. Fibrous and muscular tissues create a narrow area in some portion of the infundibulum, dividing the right ventricle into 2 chambers of unequal size, one with a hypertrophied wall, and the other dilated and thin-walled. 2. The infundibulum is shrunken in size, with thick muscular walls constituting a fusiform stenotic outlet. The authors did not encounter this second type in the 5 patients presented.

The symptoms, if any, of isolated infundibular stenosis are identical with those of valvular pulmonic stenosis and include exertional dyspnea, fatigue, syncope, dizziness, anginal pain, and, eventually, edema and right heart failure. Clubbing and cyanosis indicate the presence of a septal defect in both groups and rule out an isolated obstruction. The following points may help to differentiate infundibular stenosis from valvular stenosis: 1. Right ventricular precordial lift may be absent in very low infundibular stenosis. 2. The thrill and systolic murmur are usually maximal in the third left intercostal space in infundibular stenosis and higher up in valvular stenosis. 3. The second heart sound may be widely split in infundibular stenosis with a normal or diminished pulmonary component. 4. Usually no poststenotic dilatation of the pulmonary artery is seen on x-ray in infundibular stenosis and, in the right anterior oblique view, the left lower midsegment may bulge. 5. On fluoroscopy, the pulsations of the main pulmonary artery are increased in valvular stenosis, but not in the infundibular type. The only one of the above

features which occurred constantly in the 5 patients presented was the lower site of the murmur and thrill; these were always louder in the third than in the first space. Right ventricular hypertrophy was present in both types of obstruction. A correct diagnosis of isolated infundibular stenosis was made preoperatively in 4 of the 5 patients.

Operation was performed under hypothermia, and the obstructing tissue was resected under direct vision via a ventriculotomy. It was found that hypothermia was suited ideally for the surgical treatment of isolated infundibular stenosis, since either valvular or infundibular obstruction can be effectively and safely treated with this technique alone. As a result of the treatment, 2 of the 5 patients had mild residual gradients, 1 had no gradient but a mild pulmonary hypertension (50 mm. Hg), while the other 2 had normal hemodynamics. All the patients were much improved clinically, and it is felt that they now have cardiovascular physiology compatible with full exercise and long life. Since this report was made, 3 additional patients have been operated on by the same method with excellent results.

Clinicopathologic Correlation in Thromboembolism. W. W. Coon and F. A. Coller. Surg. Gynec. & Obst. 109:259-269 (Sept.) 1959 [Chicago].

The authors attempted to demonstrate some of the vagaries and difficulties in the diagnosis of thromboembolic disease by reviewing the autopsies of 606 patients who had died of pulmonary arterial embolism at the University Hospital, Ann Arbor, Mich., between 1945 and 1954. The clinical records of the 606 patients were assessed with regard to the severity of associated disease and the prognosis on the basis of this disease; in addition, the nature of the terminal episode and the size, number, and location of emboli were considered.

The pulmonary embolism was thought to be the sole immediate cause of death in 198 patients, a contributory factor in producing death in 190, and of minor significance in 218. In only 7.1% of the 595 patients with autopsy-proved pulmonary emboli (excluding 11 on whom medicolegal autopsies were performed) had a definite clinical diagnosis been made prior to death. The correct clinical diagnosis of venous thrombosis was made even less frequently. Of 73 patients in whom venous thrombi were found in the iliac veins or the inferior vena cava, only 37 presented clinical manifestations of deep venous thrombosis. There was no demonstrable edema or other clinical sign in the remaining 36 patients despite the fact that iliac venous occlusion was present. The authors found that there are no specific diagnostic signs in pulmonary embolism. Chest pain and hemoptysis are infrequent and, when they are present, usually reflect the presence of pulmonary infarction. The differentiation of phlebothrombosis and thrombophlebitis on the basis of embolic potential is not only fallacious but dangerous.

Some pulmonary emboli in this series had no effect with regard to the patient's ultimate survival, either because they were minor emboli or because major emboli occurred in a patient who would have died even had the embolism not occurred. Even eliminating this group, death in 6% of the entire autopsy population might have been forestalled had pulmonary embolism not been present; in a third of this group there was little question that pulmonary embolism, which should be considered as a wholly preventable disease, was the sole cause of death. The clinician must assume much greater clinical awareness of the frequency of thromboembolism and be willing to make a presumptive diagnosis and treat with anticoagulants on the basis of suspicion alone. It is only in this way that one can hope to achieve anything by this approach in the salvage of more patients from fatal pulmonary embolism.

Splenic Pulp Manometry as an Emergency Test in the Differential Diagnosis of Acute Upper Gastrointestinal Bleeding. W. F. Panke, L. M. Rousselot and A. H. Moreno. Surg. Gynec. & Obst. 109:270-278 (Sept.) 1959 [Chicago].

In an attempt to differentiate esophagogastric varices from other sites of upper gastrointestinal hemorrhage during the acute bleeding episode, the authors used emergency percutaneous splenic pulp manometry in 113 patients who had recently bled or were actively bleeding from the upper gastrointestinal tract. Thirty-three of the 113 manometric readings were obtained as the initial discriminatory test during an acute bleeding episode. The remaining 80 readings were recorded some time after bleeding had ceased. Diagnosis of portal hypertension and varices was further substantiated by portography. Pressures were determined by inserting a no. 18 gauge spinal needle into the spleen. Local anesthesia was routinely used in the adult patients. The needle was inserted 1 to 3 cm. into the splenic pulp, depending on the degree of enlargement of the spleen. A constant drip of blood from the needle usually confirmed the intrasplenic location of its point. The needle was subsequently attached to a water manometer with its zero point at table level. A short length of rubber or plastic tubing interposed between the needle and the manometer prevented a rigid system and minimized the possibility of laceration of the spleen during subsequent respiratory motions. The average of 3 sequential readings was adopted as representative of the splenic pulp pressure. The corrected baseline for transposition to portal pressure was taken at 12 cm. above the plane of the table on which the patient was lying supine.

Data obtained subsequently to manometry established esophagogastric varices as the site of bleeding in 66 patients. The remaining 47 patients bled from other lesions. Splenic pulp pressures of patients who had bled from varices were consistently higher than those of patients who had bled from other causes. The mean pressure of patients bleeding from varices was 413 mm. of water. The mean pressure of patients bleeding from other sites in the upper gastrointestinal tract was 175 mm. of water. All patients whose pressures were above 290 mm. of water had bled or were bleeding from varices. If the pressure was below 250 mm., bleeding in all instances resulted from a lesion other than varices. There remained a narrow and delimited nondiagnostic area of overlap ranging from 250 to 290 mm. of water, which included patients bleeding from esophagogastric varices as well as patients bleeding from other lesions. Eleven patients, 4 bleeding from varices and 7 bleeding from other sites, had splenic pulp pressures in this area of overlap. In these patients, the findings of serial splenoportography were ultimately essential in determining the presence or absence of varices. Sixty-two (94%) of the 66 patients who bled from varices had pressures in excess of 290 mm. of water, and often in the range of 400 to 650 mm. of water.

Excellent correlation between portal tension and the degree of portal collateralization, as revealed by portography, had previously been shown. Splenic pulp pressure has proved to be a good index of actual portal vein pressure. The results obtained with splenic pulp manometry in the 113 patients showed that this method alone may yield valuable diagnostic information as to the presence or absence of varices. The procedure has proved to be 90% accurate. It is relatively simple, direct, practical, and safe. The immediate knowledge of the presence or absence of varices gained from its use has resulted in a more accurate appraisal and a more effective management of these patients.

Late Results in 110 Patients with Abdominal Aortic Aneurysm Treated by Resectional Placement of Aortic Homograft. L. O. Sheranian, J. E. Edwards and J. W. Kirklin. Surg. Gynec. & Obst. **109**:309-314 (Sept.) 1959 [Chicago].

The authors report on 110 patients with aneurysms of the abdominal aorta, who were operated on at the Mayo Clinic between 1953 and 1957. The aneurysms were resected, and an aortic homograft was used to replace the excised vessel. One hundred four of the 110 patients had elective operations for nonruptured aneurysms, and 6 had emergency operations for ruptured aneurysms. Of the 104 patients without rupture of the aneurysm, 15 (14.4%) died in the hospital; of the 6 patients with ruptured aneurysm, 3 (50%) died in the hospital. In 8 (44%) of the 18 hospital deaths, postoperative hemorrhage related to homografting was the cause. In 5 of these, the hemorrhage was due to rupture of the homograft wall, and in 3 the hemorrhage seemed to originate at suture lines. Of the 92 patients who left the hospital after resection of the aneurysm and insertion of the homograft, 8 died in the course of the following 4 years. Failure of the homograft accounted for 3 of these deaths, occurring 2½, 1½, and 1½ years after the operation. Altogether, failures related to the use of homografts accounted for 11 (42%) of the total 26 hospital and late deaths. These 11 deaths occurred among 10% of the entire group of 110 patients treated by resection and homograft.

Of the patients surviving the operation and traced for 3 years, 84.8% were found to be living. This compares favorably with the expected 3-year survival rate of 89.5% for the normal population group at the average age of 63 years, which was the average age of the patients at operation. The survival rate of the patients with aneurysms of the abdominal aorta treated by resection and grafting was better than that in Estes' series of 102 patients with untreated aneurysms of the abdominal aorta. Homografts in the abdominal aorta, however, are not without serious specific complications, primarily rupture of the wall of the graft, which has occurred both early and late in the postoperative period. Plastic prostheses may prove advantageous in avoiding the problem of graft failure observed when homografts are used.

Valvotomy as a Curative Operation for Simple Pulmonary Stenosis. M. Campbell. Brit. Heart J. **21**:415-428 (July) 1959 [London].

Campbell considers "simple pulmonary stenosis" the best term for pulmonary valvular stenosis with a closed ventricular septum, whether the foramen ovale is unsealed, in which case central cyanosis will develop if the stenosis is severe enough, or whether it is sealed, in which case there cannot be central cyanosis, however high the right ventricular pressure. He points out that 4 years ago he, together with Brock, reported the results of pulmonary valvotomy in 58 patients with this defect. They gave the following reasons for considering this a good operation: It relieved the symptoms and cyanosis, if these were present; in addition, it enabled a large heart to become smaller and reduced the strain on the right ventricle. Campbell now reports the further progress of these 58 patients and of another 18 operated on up to the end of 1956, making 76 in all. There were 13 more acyanotic and only 5 more cyanotic patients, making a total of 46 acyanotic and 30 cyanotic. The main purpose of this study was to assess the results more critically and to consider how far pulmonary valvotomy for simple stenosis can be considered a curative operation. More patients

have been recatheterized, and the significance of the pressure reading taken at operation is now better understood. For patients who had not reached the stage of congestive heart failure, the operative mortality was under 6%. Only one patient failed to obtain any benefit, and this was because his stenosis was not recognized as infundibular.

This report is concerned chiefly with 57 patients, the others having been disregarded mostly because they were lost to follow-up. Thirty-five (61%) of the 57 patients, including similar proportions of acyanotic and cyanotic patients, improved enough to be able to lead normal lives, and none has lost any of the improvement that was gained. Another 22 patients (39%) were improved, often greatly, but they still had significant pulmonary stenosis that may prove harmful in the future. Most of the patients with the best results were under 16 years of age, and only 4 were over 20; on the other hand, nearly half of those who were only improved were over 20. One reason may be that good reduction of the gradient is more difficult because the valve and the outflow tract have become more rigid, but it is thought that sometimes it is because the fibrosis of the right ventricle has become irreversible. Therefore, patients should be operated on at an earlier age, as soon as convenient and always before they are 17. After 25 anything approaching a curative operation becomes much less likely.

The impression was gained that valvotomy should be performed on patients with less severe stenosis than existed in those operated on in the past. At first with so many patients waiting, most of those operated on had right ventricular systolic pressures of 100 mm. Hg, but Campbell now thinks that a systolic gradient of 50 mm. across the pulmonary valve indicates the need for valvotomy. Patients with an average residual gradient of less than 30 mm. have done very well, but those with one of over 50 mm. leave much to be desired. Gradients of 25 to 30 mm. are not of much importance, whether they are natural, as in cases of very slight stenosis, or residual, after surgical relief of a larger gradient. The great importance of continuing long-term studies for many years is emphasized, since there is no other way of obtaining the information that is necessary for giving the right advice to patients.

PATHOLOGY

Teratoma of the Lung. F. C. Collier, E. A. Dowling, D. Plott and H. Schneider. A. M. A. Arch. Path. 68:138-142 (Aug.) 1959 [Chicago].

The authors report a case of benign teratoma arising in the upper lobe of the left lung in a 46-year-old woman who was admitted to the University Hospital in Birmingham, Ala., in April, 1958. Eleven cases from the literature are also reviewed. Benign teratomata are mostly of the "dermoid cyst" type, i. e., consisting largely of ectodermal derivatives. The similarities of structure and symptomatology make it most likely that teratomata of the lung and the mediastinum have a common genesis. The third pharyngeal pouch, which according to Schlumberger represents the anlage of the thymus, is suggested as the most reasonable explanation of the genesis of these teratomata. The third pharyngeal pouch is entodermal, being invested by mesenchyme but also being in close contact with the cervical sinus, which is part of the ectodermal third branchial cleft. Thus, tissues from any of the 3 fundamental germ layers may be represented in these teratomata. In support of this thesis, it is pointed out that teratomata of the mediastinum always occur in the vicinity of the thymus and frequently are in intimate contact with this gland.

New Morphologic Aspects of Pulmonary Aspergillomas: Probable Initial and Residual States. J. C. Pimentel. Gaz. méd. port. 12:333-348 (March-April) 1959 (In Portuguese) [Lisbon].

From a study of 205 specimens removed during surgical operations for various pulmonary conditions, 15 cases of aspergilloma were detected. In 4 cases the pathological changes characteristic of the pulmonary aspergilloma were not translated into radiologic or clinical signs. The macroscopic examination of the specimens revealed cavities of an irregular ovoid shape, apparently epithelized, filled with a yellowish gray mass, the size of a pine cone. The cavities were lined with a layer of a similar structure, thicker at some points, creating the impression of protuberances. The pulmonary parenchyma outside the cavities presented numerous ectatic bronchi and small caseous encapsulated foci. The microscopic examination revealed a wall rich in fibrous tissue, covered with a simple cylindrical epithelium and, in small areas, with metaplastic epithelium. In one case the fungous culture permitted the identification of Aspergillus fumigatus; in the other 3 cases the sections, already fixed in Formalin, did not yield any culture. The mycelian masses presented 2 different morphologic aspects which were interpreted as the histological aspects of live and dead fungi respectively. In 3 cases both aspects were observed, while in one there was only the aspect of a live fungus.

In the other 11 specimens, classified as pathological structures of residual aspergilloma, the 2 characteristic features were a picture of infected bronchiectasis and the presence of a necrosed and softened mycelian mass in the lumen and in the granulated tissue of the ectatic bronchi. The mycelian mass had the aspect of dead fungi, and was approximately the size of a grain of corn, localized in the interior of a tuberculous cavity in full activity.

The findings are interpreted as indicating that in the pathological structure of pulmonary aspergilloma the fungus is not exactly a pathogenic agent. The process is fundamentally identical with that caused by the presence of an endobronchial foreign body. It seems that an overt antagonism exists between the fungal proliferation and a serious bronchopulmonary infection, leading to the regression of the mycelian mass. In this situation the diagnosis can only be made through a detailed microscopic study of the endocavitary mycelian mass and of the cavitary wall.

The Diagnosis of Intra-atrial Tumors and Tumor-like Formations. V. A. Zhmur. Klin. med. 37:27-34 (July) 1959 (In Russian) [Moscow].

The article analyzes observations on 6 patients with various cardiac diseases in whom autopsy demonstrated tumors of the atria. Literature data, as well as the author's observations, show that the tumors are usually myxomas, localized in the left atrium of the heart. Clinically, this disease resembles most frequently the clinical picture of mitral stenosis. Developing tumors of the atrium manifest the following syndromes: (a) obliteration of the atrial cavity; (b) occlusion of the atrioventricular orifice; and (c) embolism of vessels. On the basis of studies of the literature and the observations described, the author considers diagnosis during life quite feasible. Diagnosis during the life of the patient should direct the surgeon's endeavor to the operative removal of this neoplasm.

Malignant Pleural Mesothelioma: A Case Report With Autopsy Findings. D. S. Kahn, A. Glay and P. Madore. J. Thoracic Surg. 38:225-234 (Aug.) 1959 [St. Louis].

The authors report a primary malignant tumor of the parietal pleura in a 43-year-old man admitted to St. Mary's Hospital in Montreal in September, 1955. A thoracotomy with removal of the main tumor was performed, but diaphragmatic pleural implants precluded complete removal. The patient died one year after the operation. At autopsy, a second tumor showed a predominantly sarcomatous pattern with only rare foci of epithelium-like structure, usually in relation to free surfaces. There was widespread involvement of adjacent structures, evidence of spread through the diaphragm, and one microscopic metastatic focus in an adrenal. However, the specimen removed at operation had shown an epithelium-like structure with cells arranged in tubular and papillary fashion. There were no fibroblastic or sarcomatous features.

The controversy concerning the origin of pleural tumors centers around the necessity of explaining the 2 types of tissue, epithelial and fibrous, sometimes found in these tumors. As the tumor removed at operation had almost no fibroblastic component, consisting of cells resembling epithelial cells, and the tumor at autopsy had in the main a sarcomatous pattern with only a few epithelium-like areas, it is felt that the case reported demonstrates clearly that the epithelium-like and sarcomatous components found in primary tumors of the serosal cavities represent morphologic variations of the same neoplasm. There does not appear to be enough evidence to decide unequivocally whether these are truly primary tumors of a specialized structure, the mesothelium, with an embryonic potential to produce both epithelial and fibrous tissue elements, or whether they are fundamentally fibrous tissue tumors in which cells with an altered form, resembling epithelial cells, may be found.

Malignant synoviomas, which histologically closely resemble these pleural tumors, are accepted as fundamentally sarcomatous. The term "mesothelioma" is then probably not fully justified from an academic point of view. From a practical point of view, however, it serves a purpose in denoting a tumor arising primarily in the serosal cavities, which has a varied histological structure and which, when malignant, has a rather uniform growth pattern with extensive invasion but with little tendency to metastasize.

Observations on a Patient with the Malignant Carcinoid Syndrome. J. A. Kirkland, R. Cass, K. G. Lowe and S. F. Soutar. J. Clin. Path. 12:362-371 (July) 1959 [London].

The 62-year-old woman, whose history is presented, had had vague upper abdominal pain for about a year, and had lost weight for about 6 months. On examination, a mass was found in the right side of the hypochondrium. At laparotomy a Meckel's diverticulum, containing a hard nodule, was removed, and one of many metastatic deposits in the liver was taken for biopsy. Examination of the nodule in the diverticulm revealed that it was an argentaffin carcinoma (carcinoid tumor) which showed an unusual glandular structure. The specimen taken from the liver for biopsy revealed almost complete replacement of liver parenchyma by argentaffin carcinoma, with the same glandiform structure as was seen in the nodule in the diverticulum. The patient enjoyed reasonable health for some months, but the liver continued to enlarge and the patient needed increasing amounts of codeine for relief of pain. She died about 10 months after the operation.

During the last 9 months of the patient's life studies were made on the 5-hydroxytryptamine (5-HT) (serotonin) in her blood, and on the 5-hydroxyindolacetic acid (5-HIAA) in the urine. After death various body tissues were subjected to chemical analysis. The figures for 5-HT and for 5-HIAA obtained in this patient indicated that she had a functioning malignant carcinoid syndrome. At autopsy the 5-HT content in a lymph node

metastasis was 2 mg. per gram of tissue, that is, it was comparable to the findings in other cases of malignant carcinoid syndrome.

Special attention was paid to the staining properties of the tumor cells because of the suggestion by others that there are argentaffin and argyrophil types of tumor cells. It has also been suggested that argentaffin cells secrete 5-hydroxytryptamine (5-HT) and argyrophil cells secrete 5-hydroxytryptophan (5-HTP). Comparison of various staining methods (including the silver methods) and the various fixatives used, with particular note of the cytological quality of the sections, led the authors to conclude that the new method of Lendrum and Fraser is more informative. Studies on the tumor cells suggested that there is only one type of neoplastic cell. In the lung and in the arterioles, histological changes were observed that may be a clue to the pulmonary hypertension of the carcinoid syndrome. It is suggested that the circulating 5-HT might act on the elastica of the pulmonary vessels and thus be the first link in the chain of causation of the pulmonary hypertension.

Latex-Fixation Test in Rheumatoid Arthritis: I. Clinical Significance of a Thermolabile Inhibitor. A. F. Schubart, A. S. Cohen and E. Calkins. New England J. Med. **261**:363-368 (Aug. 20) 1959 [Boston].

The authors studied the serums obtained from 418 patients with articular disease seen at the arthritis clinic of the Massachusetts General Hospital, Boston, and from 360 patients seen at the medical clinic of this hospital, with the aid of the latex-fixation test (F-II L. P. test), both before and after heat inactivation at 56 C (132.8F) for 30 minutes. The results showed a striking difference between the native and inactivated serums. In many, a prozone inhibition was present, usually in dilutions of between 1 to 10 and 1 to 640. In the serums of 25 of 177 patients with definite rheumatoid arthritis, i. e., in significant numbers, total inhibition was present in the native serum, whereas, after heat inactivation, a positive reaction of the serum to the test was found in titers as high as 1 to 5120. Total inhibition was also seen in serums of patients with rheumatoid spondylitis, lupus erythematosus disseminatus, chronic rheumatic heart disease, ochronosis, leprosy, nontoxic goiter, diabetes mellitus, and several other diseases.

The reported results indicate that the thermolabile inhibitor may be demonstrated in any serum that contains agglutinating activity in the F-II L. P. test. The advantage of heat inactivation of the serum seems to be predominantly that of eliminating an unstable factor from a serologic system and thus increasing the reproducibility of the tests, which become more sensitive with an apparent loss of specificity. The latex-fixation test was slightly modified in the authors' study by reduction of centrifugation speed to accentuate the inhibition phenomenon. An increase in the concentration of gamma globulins used resulted in reduction of inhibition. The decrease of gamma globulin concentration created a higher degree of inhibition. The frequency of positive F-II L. P. tests in various rheumatic diseases, as well as certain other disorders, stresses the nonspecific nature of the test. The relation between duration and activity of disease and titer in the F-II L. P. test has not yet been fully clarified. Pending further data on this point, it appears that detailed classification of patients, as well as standardization of the method of the test, is desirable to produce results that are comparable.

Histophysiology of the Adrenal Cortex and Medulla in Carcinoma of the Breast: Researches in Adrenalectomized Women. J. V. Frazão and L. Botelho. Arq. pat. **31**:261-334 (March) 1959 (In Portuguese) [Lisbon].

Ten women, between the ages of 36 and 65 years, with cancer of the breast and metastases, were treated by adrenalectomy in the Instituto Português de Oncologia, in Lisbon. The patients had metastases in the lymph nodes and the bones, and some even in the adrenals. Five patients had had a mammectomy alone which was followed by roentgen-ray treatment, 4 had had only roentgen-ray treatment, and 7 had had bilateral ovariectomy. Adrenalectomy was bilateral in 7 patients, and unilateral in 3. When bilateral, the right adrenal had been surgically removed 3 weeks after removal of the left. The adrenal glands of these patients showed histopathological changes in both the cortex and the medulla similar to changes which the structures undergo in the presence of other diseases caused by stress. The adrenal cortex reacted to cancer as it usually reacts to hypertension, hypertrophy of the heart, or the Winiwarter-Buerger disease, whereas the adrenal medulla reacted to cancer as the adrenal medulla of animals usually reacts to poison gases.

The authors conclude that cancer is a disease due to chronic stress. The adrenals play a role in the evolution of cancer and of its metastases by stimulating hypersecretion of stress substances from the anterior part of the pituitary. In patients with cancer of the breast with metastases, the stress diminishes after adrenalectomy, thus resulting in great improvement of the acute symptoms.

RADIOLOGY

Potentiation of X-Ray Effects by Actinomycin D. G. J. D'Angio, S. Farber and C. L. Maddock. Radiology **73**:175-177 (Aug.) 1959 [Syracuse, N. Y.].

The authors report on 126 children and adults who received 220 courses of roentgen irradiation combined with the intravenous administration of

actinomycin D, an antibiotic and carcinolytic agent, at the Children's Cancer Research Foundation of the Children's Medical Center in Boston. The following observations were made. Some neoplasms, such as the malignant melanoma, usually considered to be radioresistant, responded well to combined therapy in some patients. The most favorable responses were obtained in patients with nephroblastoma (Wilms's tumor), Ewing's sarcoma, hemangioendotheliosarcoma, and rhabdomyosarcoma, definite improvement resulting after about 75% of the courses of combined therapy given to these patients. Simultaneous chemotherapy and irradiation therapy in low doses appear to be as effective as higher doses of either modality in certain instances. There is some evidence for a longer lasting beneficial effect with combined therapy. There is no apparent "cross resistance" between the 2 forms of therapy, even though it would appear that there is some gross similarity between some of their methods of action. Neoplasms may develop a resistance to the combination of agents, after which they are also refractory to either one alone. Potentiation of roentgen irradiation effects on normal tissues did not limit the total amount of roentgenotherapy that could be given to any patient. Interruptions to allow recovery, however, were not infrequent. Striking effects were obtained in tumors without apparent enhanced reactions in the skin or mucous membranes.

These findings suggest that irradiation responses in normal tissues and certain malignant tumors are enhanced when roentgen irradiation is combined with intravenous administration of actinomycin D. Normal structures react after smaller doses of irradiation than are ordinarily required to produce a like effect, and the healing processes thereafter proceed at a more rapid rate. Actinomycin D alone can reactivate latent irradiation effects in tissues which have been previously irradiated but have returned to normal in appearance. The reaction grossly is identical in type and distribution to that produced by the roentgenotherapy given earlier.

Modification of Late Irradiation Injury with L-Triiodothyronine. A. S. Glicksman, R. W. Rawson and J. J. Nickson. Radiology 73:178-190 (Aug.) 1959 [Syracuse, N. Y.].

Some of the authors initially noted in patients with carcinoma of the thyroid, who had severe irradiation changes of the skin and subcutaneous tissues, that production of hyperthyroidism seemed to produce a beneficial effect on these postirradiation changes. In an attempt to explore the role of exogenous thyroid hormones in the management of established irradiation damage, 75 patients in the irradiation damage clinic of the Memorial Center for cancer and allied diseases in New York were treated with liothyronine (3,5,3'-L-triiodothyronine [T-3]), which was selected because of the rapidity of its action as well as the promptness with which it is excreted by the body. The patients were started on 25 mcg. of the drug, given twice daily, and this dose was gradually increased to 200 mcg. per day, according to clinical judgment. Some patients were carried on 200 mcg. per day for more than 2 years. Of the 75 patients, 46 had ulcerations of the skin and subcutaneous tissues 2 to 20 years after irradiation, 24 had late irradiation fibrosis, and 5 had pulmonary fibrosis. Of the 46 patients, 13 were lost to follow-up, and of the remaining 33 who received T-3 for periods long enough to warrant evaluation, 10 showed excellent improvement, 18 good improvement, and 4 fair improvement; the condition of one was made worse. Of the 24 patients with late irradiation fibrosis, 8 were lost to follow-up, and of the remaining 16, 4 showed an excellent response, 7 a good response, 2 a fair response, and 3 were therapeutic failures. Of the 5 patients with pulmonary fibrosis, 1 was lost to follow-up, 1 showed good response with return of maximum breathing capacity to preirradiation levels, 1 showed only fair response, and 2 were therapeutic failures. Of the patients with damage being present from 2 to 30 years, over 50% showed good to excellent response to T-3 therapy. This would indicate that late irradiation changes exist in a dynamic state and that it is possible to modify them by altering the metabolism of the damaged tissue.

Supervoltage (2-Mvp) Rotation Irradiation of Cancer of the Bladder. M. Friedman. Radiology 73:191-208 (Aug.) 1959 [Syracuse, N. Y.].

The author presents a preliminary report on 81 patients with cancer of the urinary bladder, who were treated with 2 million volt x-ray irradiation by the rotation technique in the radiation therapy department of the Hospital for Joint Diseases in New York between 1951 and 1958. The patients had been subjected previously to various types of surgical procedures, and most of them had extensive and advanced lesions. Twenty-one patients (25%) had primary tumors, and 60 (75%) had recurrent tumors. The patient stood erect on a rotating platform during supervoltage irradiation; the target axis distance was 125 cm., and the exposure dose rate at the axis of rotation was 57 rads (units of measurement of the absorbed dose of ionizing irradiation) per minute. In most patients the field size at the axis of rotation was 8 by 8 cm. Occasionally when an advanced cancer infiltrated the pelvis, the field size was enlarged to 12 or 15 cm. in horizontal diameter. Its vertical height was seldom higher than 10 cm. because of the danger of irradiation injury to the small intestine.

A 3-year survival rate of 22% and a 5-year survival rate of 13% were obtained with the supervoltage rotation irradiation technique in this group of patients. Doses of from 8,000 to 10,000 rads, given within 40 to 60 days, proved successful. An occasional patient required larger doses. These doses are higher than those reported by other workers. Their use was dictated by the findings at serial cystoscopic examination, followed by biopsy, during treatment, and by the frequent finding of residual disease after the administration of doses ranging from 7,000 to 8,000 rads. The author cannot yet reconcile his large doses with the smaller doses reported by other workers, but he believes that advanced highly malignant cancers of the bladder require large tumor doses. These large doses can be given only with a well-collimated beam of supervoltage x-rays or gamma rays, with a precision beam-aiming technique. In order to improve the results of irradiation of cancer of the bladder, the prevalent practice of multiple surgical procedures preceding the irradiation will have to be discontinued, and irradiation started when the disease is in an earlier phase. Radiation cystitis is more severe after supervoltage rotation irradiation than after irradiation performed with the central-source intracavitary technique. The irradiation results in the patients treated for primary tumors with a 3-year survival rate of 42% were better than in those treated for recurrent tumors with a 3-year survival rate of 18%.

The unusual case of a 35-year-old woman is described; this patient had a grade 3, large, fungating, infiltrating carcinoma on the left lateral wall of the bladder which was radioresistant. She was given a maximum tumor dose of 13,200 rads in 90 days, and the disease was controlled. Injury to the intestines was corrected surgically, and the patient is alive without evidence of cancer 6 months after the completion of the supervoltage rotation irradiation treatment. However, comparison of the results of the supervoltage rotation irradiation in this group of 81 patients with those in a group of 50 patients treated by the author with central-source intracavitary irradiation has suggested that the latter technique is superior to supervoltage rotation irradiation for cancer of the bladder, since it yielded a 5-year survival rate of 56% as compared with the 5-year survival rate of 13%.

Supervoltage Irradiation in Bladder Carcinoma: 1952-1958. P. Rubin and R. Buran. Radiology 73:209-225 (Aug.) 1959 [Syracuse, N. Y.].

The authors report on 51 male and 10 female patients with carcinoma of the bladder, most of them between the ages of 60 and 80 years, who were treated with one million volt x-ray irradiation by the rotation technique at the Strong Memorial Hospital in Rochester, N. Y., between 1952 and 1958. The commonest presenting symptoms were hematuria (57%), frequency (51%), and dysuria (38%). Nocturia occurred in 16%, and pain in 15%. On cystoscopic examination 38 (63%) of the 61 patients had multiple lesions as opposed to solitary papillary lesions. The most frequent anatomic sites of origin were the trigone (33%) and bladder neck (33%), followed by the lateral walls (21%) and diffuse involvement (16%). The fundus was involved in 5%, the posterior wall in 7%, and the anterior wall in 5%. The daily tumor dose generally was 200 r at the axis of rotation, and the total dose administered to these patients ranged from 5,000 to 6,000 r in 5 or 6 weeks, with doses of 3,000 to 4,000 r reserved for palliative rather than curative purposes. The field size usually ranged from 8 by 8 to 10 by 10 cm. If extensive pelvic disease was present, larger fields, up to 15 by 15 cm., were employed. Cystoscopy was performed at the end of the treatment, with repeat examinations scheduled every 2 to 4 months during the first year and at lengthening intervals as the disease appears to be controlled.

The results obtained in these patients warrant the following conclusions. The principles of treatment of tumors of the bladder are dependent on the classification of each patient according to primary and secondary considerations. For group 1, consisting of patients with superficial-stage, low-grade carcinoma, the initial treatment of choice is a conservative surgical measure, such as fulguration, transurethral resection of the tumor, or segmental resection. As the lesions recur, become multiple in origin, and change their histological grade and depth of invasion, more radical measures are justified. Supervoltage irradiation should be employed only as an alternative to total cystectomy and not as a prophylactic measure. Sixteen of the 61 patients were in this group; 6 patients were controlled by irradiation, and 5 survived without disease for periods ranging from 6 months to 4 years and 3 months. For group 2, consisting of patients with deep-stage, high-grade carcinoma, supervoltage irradiation in curative dosage levels has the most to offer those with deeply invasive and aggressive tumors. Results suggest that cure rates are at least comparable to, and perhaps better than, those obtained by radical surgical procedures, with less morbidity and mortality. There were 26 patients in this group; 10 of them were controlled by irradiation, and 5 survived without disease for periods ranging from 2.3 to 5 years.

In group 3, consisting of patients with metastatic-stage, high-grade carcinoma, supervoltage irradiation as a palliative procedure can control pain and hematuria and is more easily tolerated than orthovoltage therapy. A diversionary measure, as an ileal bladder and ureteral transplantation, may be equally or more palliative in many cases than moderate doses of irradiation. In selected patients an ileal

bladder may enable one to deliver a curative dose of irradiation and perhaps sterilize the primary lesion. There were 19 patients in this group, 18 of whom died and 1 is alive with persistent carcinoma. Any modality of treatment, including supervoltage radiation therapy, failed. Last and of most importance are cooperation between the patient and the physicians responsible for treatment and follow-up and cooperation between the urologist and the radiologist, since in a large number of patients more than one modality of treatment will be used.

Percutaneous Splenoportography: Evaluation of Clinical Indications: Importance in the Study of Portal Hypertension. C. Larrain, C. Zuñiga, G. Labatut and others. Rev. méd. Chile. 87:410-420 (June) 1959 (In Spanish) [Santiago].

Percutaneous splenoportography was performed on 56 patients hospitalized in the Hospital Aguirre of Santiago, Chile. A percutaneous injection of an opaque substance was made into the spleen during a period of 9 seconds, roentgenograms being taken at the 3rd, the 6th, and the 9th second after the injection. Normal features of splenoportography were shown by an even opacification of the entire splenoportal system, including the fine intrahepatic portal branches, within 3 seconds after the injection. There were no splenoportal collaterals, and the lumens of both the splenic vein and the portal vein were normal. In portal hypertension the splenoportal system became opacified within 6 to 9 seconds after the injection, with faint showing of the fine intrahepatic portal branches. The splenoportal venous system was hypertensive, and there were engorged collaterals and varices.

Splenoportograms showed that, of the 56 patients, the splenoportal system became opacified in 51. Thirty-five of these patients had cirrhosis of the liver, and 28 had signs of portal hypertension in that they had had hemorrhages by mouth. Roentgenologic examination of the esophagus and endoscopy showed esophageal varices in 16 patients. Splenoportography showed a normal condition in 9 of the 35 patients with chronic cirrhosis of the liver, and in the remaining 26 it showed esophageal varices and splenoportal collaterals which had not been shown by roentgenologic examination of the esophagus or by endoscopy. Splenoportography was also of diagnostic value in patients with chronic myeloid leukemia, intrahepatic metastases of gastric carcinoma, and hydatid cysts of the liver. It followed a normal pattern of opacification in patients with liver abscesses, splenomegaly of uncertain origin, abdominal lymphosarcoma, alcoholic gastritis, and fatty liver. Percutaneous splenoportography is of value in the diagnosis of portal hypertension of either intrahepatic or extrahepatic origin. The procedure is harmless and is well tolerated by the patients.

Pulmonary Staphylococcia: Clinical, Radiologic, and Therapeutic Study. A. Roisinblit, L. Anunziato and W. E. García. Prensa méd. argent. 46:630-638 (March 13) 1959 (In Spanish) [Buenos Aires].

In the differential diagnosis of pulmonary staphylococcia, the radiologic aspects represent an important element, since the clinical picture is very similar to that of other lung diseases. The authors report 3 cases in which serial radiograms permitted the establishment of the diagnosis and the administration of adequate therapy. The radiologic signs are generally present from the 5th day after the onset of the disease, and they include pneumothorax, pneumatocele formation, variable infiltration with perifocal emphysema, early encapsulation of pleural effusion, and hilar enlargement.

The first patient, a 27-year-old woman, felt ill, with hypogastric pain, fever, and metrorrhagia, 24 hours after an induced abortion. As she subsequently developed dyspnea, oliguria, and jaundice, a radiologic examination showed signs of staphylococcic infection of the lungs, which was confirmed by the finding of Staphylococcus aureus in the sputum. The patient received Sigmamycin (a combination of oleandomycin and tetracycline) orally, then erythromycin. Although her condition improved, the same radiologic alterations persisted. As she refused surgical treatment, she was discharged from the hospital. Her condition deteriorated again, the clinical picture being that of septicemia, and the blood culture being positive for Staph. aureus. The intravenous administration of Sigmamycin brought temporary relief, but the patient died of blood dyscrasia. The second and third patients had similar radiologic signs of bilateral infiltration and cavitations. Antibiotic treatment (including Sigmamycin in one of the cases) resulted in recovery of both patients.

The authors insist on the necessity of taking into consideration the possibility of pulmonary staphylococcic infection in any case of acute lung disease. They consider the intravenous administration of Sigmamycin the most effective therapy available at present.

Aberrant Pancreatic Tissue in the Stomach. D. R. Rooney. Radiology 73:241-244 (Aug.) 1959 [Syracuse, N. Y.].

The author reports on 5 women and 2 men, between the ages of 32 and 71 years, with aberrant pancreatic tissue in the stomach. The commonest symptom usually ascribed to this condition is nonspecific epigastric pain; 6 of the 7 patients had this complaint. Pyloric obstruction is probably the next common symptom, and one of the patients had symptoms suggestive of partial intermittent obstruction with occasional attacks of distention. The roentgenologic findings in the 7 patients were strikingly similar. There was a solitary, sharply

demarcated, round or oval filling defect, measuring 1 or 2 cm. in diameter and located for the most part in the gastric antrum within 6 cm. of the plyoric orifice. The distinguishing morphologic finding in aberrant pancreatic tissue in the stomach is a central duct structure which is not present in other intramural gastric tumors. When the radiologist finds a filling defect, such as the one described above, a careful search, aided by pressure spot-films, should be made for a central dimple in this nodule. This central pit or depression, when visualized, encourages the preoperative diagnosis of aberrant pancreatic tissue in the stomach, since this depression surrounds the orifice of the duct draining the aberrant pancreatic acini. This central duct was identified in the gross surgical specimens from each of the 7 patients. The visualization of this structure may be of great value to the radiologist and gastrocopist in the preoperative diagnosis, and to the surgeon or pathologist who may be confronted, in the operating room, with the decision of simple against radical gastric resection.

ANESTHESIA

Apnea Associated with the Intraperitoneal Use of Neomycin. C. H. Fredell and B. L. McElroy. Southwestern Med. 40:503-504 (Aug.) 1959 [El Paso, Texas].

The intraperitoneal instillation of neomycin has been of definite value in lowering the mortality rate due to peritonitis, but reports of apnea associated with the intraperitoneal use of neomycin have been published. Experimental work has been done to elucidate the etiology of this phenomenon. The action of neomycin seems to be a potentiation, or a combination, with the anesthetic agent, producing a neuromuscular blocking effect. The presence of peritoneal damage, however, allows more rapid absorption of the neomycin, consequently lowering the amount which might produce apnea. Experimental and clinical work has shown that the apnea can be treated effectively with neostigmine methylsulfate. Two cases are presented, demonstrating this unusual problem. The authors conclude that the dangers of the intraperitoneal instillation of neomycin during a general anesthesia, in the presence of peritoneal damage, far outweigh any benefits accrued by this practice.

The Combined Preparation Penicillin-Streptomycin-Procaine Hydrochloride in Local Anesthesia. C. Buccellato, A. Cittadini and F. Gargano. Minerva chir. 14:475-480 (May 15) 1959 (In Italian) [Turin, Italy].

The authors experimented, in vitro and in vivo, with the combined preparation penicillin-streptomycin-procaine hydrochloride for use as a local anesthetic in man. The experiments in vitro revealed that the combined antibiotic action of penicillin and streptomycin in a solution of either sodium chloride or procaine hydrochloride had a similar inhibitive action on the growth of a culture of staphylococcus pyogenes var. aureus. The experiments in vivo on 8 rabbits demonstrated that the combined preparation penicillin-streptomycin in a solution of either sodium chloride or procaine hydrochloride had the same degree of inhibitive action on the development of subcutaneous abscesses, which were induced by inoculation of a suspension of Staph. pyogenes var. aureus. The anesthetic action of procaine hydrochloride did not diminish because of its combination with the antibiotics.

The combination of penicillin, streptomycin, and procaine hydrochloride was then tested with patients under local anesthesia in 30 operations. No antibiotics were administered after the operation, and the operative wounds healed fast and in asepsis. The authors believe that the combined preparation penicillin-streptomycin-procaine hydrochloride has a twofold advantage: 1. A single administration of the preparation exerts simultaneously both anesthetic and antibiotic effects, which procedure saves time. 2. There is a more effective antibiotic action of penicillin and streptomycin if administered in combination with procaine hydrochloride.

PUBLIC HEALTH

Infectious Encephalitis in Colorado. L. E. Giddings, S. G. Copps and C. A. Sooter. Pub. Health Rep. 74:647-652 (July) 1959 [Washington, D. C.].

The authors report on the epidemiologic aspects of 258 cases of infectious encephalitis which occurred in Colorado between May, 1956, and December, 1957. Most of these cases occurred in the late summer and the early fall months of the 2 years. The ages of the patients ranged from 6 days to 82 years, but there was a marked preponderance of patients less than 20 years of age. As a rule, the cases of infectious encephalitis were roughly distributed in proportion to population density throughout Colorado. Serologic tests for various causative agents were performed. The causative agent was determined by laboratory or clinical means in 109 of the 258 cases. Arthropod-borne diseases, such as St. Louis encephalitis and western encephalitis, accounted for 73 of the 109 cases, while mumps accounted for 24 and miscellaneous agents for 12. The causative agent was unknown in 149 (57.8%) cases. There were 10 deaths among the 258 patients.

Comparison of the epidemiologic characteristics of the viruses of St. Louis encephalitis, western encephalitis, and mumps, which were the com-

monest causative agents, showed that the St. Louis encephalitis virus tends to infect persons of all ages, with a slight preference for the older age groups. The age distribution was somewhat alike for the western encephalitis and mumps viruses in that the diseases occurred primarily in persons aged less than 20 years. Mumps is a highly infectious disease, endemic in most areas of the country, which becomes epidemic whenever a sufficient number of persons who are not immune are present. As a result of the frequent epidemics, most persons become immune before reaching an advanced age. The incidence of St. Louis encephalitis and western encephalitis in a community is dependent on mosquito populations and mosquito infection rates and many other poorly understood factors. In the light of present-day knowledge, the age distribution differences between St. Louis encephalitis and western encephalitis cannot be explained. The preponderance of male patients infected with the St. Louis and western viruses could possibly be explained by the fact that men and boys, in general, spend more time out-of-doors and are, hence, at greater risk of exposure to infective mosquitoes. More diagnostic work needs to be done in the field of infectious encephalitis in order to evaluate the problem brought about by the large number of agents which can produce this syndrome.

Statistical Relevances on the Behavior of Brucellar Infection During the Period 1948-1957. A. Pane and G. Manzillo. Acta med. ital. 13:144-151 (June) 1958 (In Italian) [Rome].

Italy, according to a report of the World Medical Association, had 6,914 cases of brucellosis in 1955; it was the country with the highest frequency in an absolute sense, and it came after Argentina and Malta in relative frequency. The authors report on a statistical study of 467 patients with brucellosis who were observed from 1948 to 1957 at the "D. Cotugno" Hospital of Naples, where patients with this disease from both the city of Naples and the whole Campania region are treated. Brucellosis was most frequent in 1951 and 1953, 75 cases and 60 cases, respectively, being reported; it was least frequent in 1957, with 30 cases. An increase in the frequency of most infectious diseases was observed in 1953. Data for the years 1951-1957 showed that the highest monthly frequency occurred during April, May, June, and July, with 40, 46, 50, and 44 cases, respectively, which makes brucellosis a seasonal disease most frequent in the spring and summer. Two hundred ninety-four (62.95%) of the 467 patients were male, and 173 (37.05%) were female. Seventy-six patients were 15 to 20 years of age; 69 were 20 to 25; 61 were 11 to 15; 53 were 26 to 30; 26 were 6 to 10; 19 were 1 to 5; and 12 were 61 to 75. Data on brucellosis for the whole of Italy show that there has been a slight decline in the morbidity rate during the last few years.

British Standard Poliomyelitis Antisera Types 1, 2, and 3. F. T. Perkins and D. G. Evans. Brit. M. J. 1:1549-1553 (June 20) 1959 [London].

Standard antiserums to each of the 3 poliomyelitis virus types would make it possible to express the neutralizing potency of other serums in terms of the standard and allow a valid comparison to be made between the results obtained by different workers. In 1955 reference poliomyelitis antiserums were prepared to serve as controls in titrating poliomyelitis antibodies in both human and animal serums, but these antiserums were used essentially in insuring the consistency of the titration system and not in assaying serums in terms of units. For a number of reasons they were unsuitable for use as standards to which a unitage could be assigned. New freeze-dried preparations of antiserums to each of the 3 poliomyelitis virus types were, therefore, made.

A collaborative study, in which 5 laboratories took part, showed that close agreement was obtained among the different laboratories when the type 1, 2, or 3 neutralizing potencies of poliomyelitis antiserums were determined with reference to freeze-dried preparations of antiserums. It was, therefore, decided, with the agreement of those who participated in the study, to establish the 3 freeze-dried preparations of antiserums as British standard poliomyelitis antiserums, types 1, 2, and 3, and to assign to each a value of 10 units per ampul. It will now be possible to express the neutralizing potency of serums in terms of units and to abandon the unsatisfactory method of using titer-dilutions. The standard antiserums will be held by the department of biological standards, National Institute for Medical Research, Mill Hill, London.

The Question of Poliomyelitis Infection Among Hospital Personnel. P. Sachtleben and A. Schellenberger. Deutsche med. Wchnschr. 84:1142-1145 (June 19) 1959 (In German) [Stuttgart, Germany].

Every year a certain percentage of the population, particularly children, become infected with the virus of poliomyelitis, but the infection usually remains silent. Nevertheless, it is likely that a number of children in hospitals will excrete the virus, even though they show no active signs of poliomyelitis. This suggests that exposure is particularly great among the personnel of children's hospitals. In 1956 the authors made 3 determinations of complement-fixing antibodies against poliomyelitis on the venous blood samples of 65 persons on the staff of the Children's Clinic of the University of Munich. Physicians, nurses, and physical therapists were in-

cluded. Forty-four children and 71 adults served as control groups. Physicians and senior nurses showed the same percentage of positive complement-fixation reactions (16%) as did the control group of adults, whereas among the young student nurses and the physical therapists in training the percentage was 50%. A diagram recording the seasonal incidence of positive poliomyelitis complement-fixation tests in the various groups shows an increase from summer to fall and a slight decrease from fall to winter. Discussing the cause of the differences between older and younger hospital personnel, the authors assume that the type of work performed, as well as the immunobiological processes, play a part. They assume that young adults contract chiefly first infections and heterologous reinfections, whereas in older persons (physicians and senior nurses) homologous reinfections are more frequent.

The Tetanus Problem in the South. A. N. Houston, W. A. Roy, R. A. Faust and D. M. Ewin. J. Louisiana M. Soc. **111**:241-245 (July) 1959 [New Orleans].

Taking the figures available from 1952 through 1956, the death incidence of tetanus in the United States is 0.19 per 100,000 population. During these 5 years, 1,543 persons died of this disease in the United States, with an average of 309 deaths per year. The unequal geographical distribution of the incidence of tetanus, however, may be illustrated by selecting the 11 "Confederate States" as one area, and the 37 states remaining as a comparative area. The former contained 24% of the population of the United States but had 63% of the deaths from tetanus. This means 0.50 deaths per year per 100,000 population for the "Confederate States" compared with 0.09 for the other 37 states and 0.19 for the United States at large. Louisiana, fourth in the United States with regard to deaths per 100,000 population per year, led the nation for the single year 1956 with 0.72 deaths per 100,000 population. A campaign to warn and educate all in regard to the alarming prevalence of tetanus in Louisiana and the 11 "Confederate States" has been launched and emphasis has been laid on the need for protection against tetanus. A "suggested guide" has been put out by the committee on tetanus protection of the Orleans Parish Medical Society and the committee on trauma of the Louisiana chapter of the American College of Surgeons, concerning wound care and adequate basic and booster immunization with tetanus toxoid. Antitetanic serum (or tetanus antitoxin) does not attack the causative agent, Clostridium tetani, but merely neutralizes the toxin being produced by living organisms. This serum is most often of equine origin, and, because of the discomforts of the highly prevalent types of serum sickness or the dangers of anaphylaxis, it should not be given unless real indications exist. Antibiotics have no effect on the toxin already produced by living organisms; they attack only the organisms and do so best when given within a few hours of wounding and for some days thereafter.

The Incidence of Certain Endemic Enteric Virus Infections in Southern Louisiana. H. M. Gelfand. South. M. J. **52**:819-827 (July) 1959 [Birmingham, Ala].

The author investigated the natural transmission of poliomyelitis viruses in 115 newborn children who were under the continuous observation of the epidemiology division of the Tulane University School of Medicine in New Orleans during the period from 1954 through 1956. Four hundred seventy-two serum specimens, obtained from members of the children's families or close associates, were collected and tested for their ability to neutralize prototype poliomyelitis virus strains. Findings showed a prevalence of neutralizing antibodies against poliomyelitis viruses, types 1 to 3, Coxsackie viruses, group A, type 9, and group B, types 1 to 5, and enteric cytopathogenic human orphan (ECHO) viruses, types 1 to 3, 5 to 12, and 14. Of the types investigated, only antibodies against ECHO viruses, types 4 and 13, were lacking in a final serum dilution of 1:10. There was a great variety in the age pattern of these several antibodies; some were similar to poliomyelitis virus, type 1, and others were markedly different. There appeared to be 4 general types of age-pattern curves, with several viruses represented by each. It has been suggested that these differences were more likely the result of variations among the types in the duration of detectable antibody than of variations in the ease of transmission within households.

Six hundred thirteen enterovirus strains were isolated from fecal specimens obtained from the 115 children. The poliomyelitis viruses, Coxsackie viruses, ECHO viruses, and adenoviruses were found most frequently, whereas some types were not isolated at all. The 3-year average of the percentages of children excreting viruses of all the isolated types by month shows a consistent seasonal variation, with maximal occurrence in summer and early autumn. There was a marked increase in transmission during the warmest months of the year. The interesting exception was ECHO virus, type 10, for which isolation was maximal during the winter months. No significant central nervous system or intestinal disease occurred coincidentally with these infections. The occurrence of an "epidemic" of ECHO virus, type 7, during 1956, which involved 34% of the children in this series, reemphasizes the caution that must be observed when these agents are isolated during an investigation of outbreak of disease.

BOOK REVIEWS

The Onset of Stuttering: Research Findings and Implications. By Wendell Johnson and associates. Cloth. $5. Pp. 243. University of Minnesota Press, Minneapolis 14; Oxford University Press, Amen House, Warwick Sq., London, E. C. 4, England; Thomas Allen, Ltd., 266 King St., W., Toronto, Canada, 1959.

In approaching the problem of stuttering the author brings out the following two important points: first, that the label of stutterer is usually placed on a child by a lay person and, second, that many people other than those who are really informed on this problem presume to explain it and to suggest remedial procedures. The fact that a person is called a stutterer because someone thinks he is a stutterer suggests that the problem may sometimes be with the observer rather than with the child said to have the speech problem. The book contains complete reports on three extensive studies carried out at the University of Iowa under the direction of the author. A series of 500 children and their parents were included in the investigations, one half of the children having been classified as stutterers and the other half having been considered to have normal speech. The groups were carefully matched. With use of standard tests and complete as well as careful interviewing techniques, comparative data were gathered in reference to many factors which have been thought to be causative. The author states his purpose as being "to gather substantially more of the facts to be explained before yielding further to the manifestly human compulsion to make explanations."

The mass of data collected indicated that stutterers are really not different from nonstutterers but that their speech is initially perceived and evaluated differently, usually by a parent. The negative evaluations and misperceptions of the adults are communicated to the children, who then view their own speech in this same anxious and rejecting manner. The role of the listeners in fixing and intensifying nonfluencies in particular children, who are probably in reality having no more hesitations and repetitions than any other children learning oral language, has strong implications for all persons who are responsible for children, both professional and nonprofessional.

This book merits careful attention because the author has devoted much of his career to studying and thinking about the problem of stuttering. He has been the director of the speech clinic of the State University of Iowa where more research on stuttering has been produced over a longer period of time than at any other university. In a field in which there have been strong differences of opinion, it is satisfying to have an author present his rationale, his methods, and his data so completely. Misperceptions of stutterers by professional persons can place heavy burdens on the shoulders of children and their parents. Before "yielding further to the manifestly human compulsion to make explanations" it would be well for professional persons to read this book.

Physiology of Motion Demonstrated by Means of Electrical Stimulation and Clinical Observation and Applied to the Study of Paralysis and Deformities. By Dr. G. B. Duchenne. Translated and edited by Emanuel B. Kaplan, M.D., Attending Orthopedic Surgeon, Hospital for Joint Diseases, New York. Cloth. $11. Pp. 612, with 101 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1959.

This translation makes some extremely interesting material available to readers who in the past may have been entirely unacquainted with the work of Duchenne or have had access only to translations of selected portions of his book. It is at once a compendium of detailed information and a mine of inspiration. Part 1, Motion of the Thoracic Extremity, is a fine analysis of the individual muscles of the hand, forearm, arm, and shoulder. Part 2, Movements of the Abdominal Extremity, deals similarly with the muscles of the foot and leg and those that move the thigh on the pelvis. Part 3 analyzes the action of the muscles that govern respiration and those that move the craniovertebral column.

The translator's introduction should be read for proper appreciation of Duchenne's originality. Duchenne worked on living subjects as well as cadavers, on animals as well as man, on the normal as well as the abnormal, and with electrical stimulation as well as voluntary movements. He showed how diverse are the movements obtainable from any given muscle when the position of the body is varied and how paradoxical the movements may seem when the muscle contracts in the absence of cooperation from its normal synergists and antagonists. The author's original illustrations are reproduced. They are somewhat primitive and not very numerous, but the text makes up for this lack by its vivid writing and the abundance of specific instances for every generalization. The translator has solved some difficult problems, especially that of rendering the anatomic names of muscles as written in French in 1867 into terms intelligible to readers of present-day English. The informed reader should

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recognize the phrase "muscular conscience" on page 561 as corresponding to the present term "proprioception" and will not likely be confused by the rendering of "disgraceful" on page 600, where the meaning intended was presumably "ungracious."

Medical students who are well along in the study of anatomy might do well to sample the pages of this book so as to gain an appreciation of the complexity of muscle action. The brief statements on this subject in most textbooks are necessarily simplified. To physicians and all others working in the field of physical medicine and rehabilitation, this book is highly recommended.

Synopsis of Ear, Nose, and Throat Diseases. By Robert E. Ryan, B.S., M.D., M.S. (ALR.), Associate Otolaryngologist, St. John's Hospital, St. Louis, William C. Thornell, A.B., B.M., M.D., Assistant Professor, Department of Otolaryngology, Cincinnati College of Medicine, Cincinnati, and Hans von Leden, M.D., F.A.C.S., F.I.C.S., Assistant Professor of Otolaryngology, Northwestern University Medical School, Chicago. Cloth. $6.75. Pp. 383, with 59 illustrations. C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3; Henry Kimpton, 134 Great Portland St., London, W. 1, England, 1959.

This well-illustrated and finely printed volume, with its maroon color and black label with gold lettering, is pleasing to the eye, while the size permits it to be carried comfortably in the coat pocket. The book is well designed and well written and should fill the needs of the student, intern, resident, and general practitioner. Since most patients seen by the general practitioner each day present some disorder of the ear, nose, throat, or respiratory system, it is fitting that such a work should be available to him for guidance. In fact, this book could easily rank in value with the sister volume in ophthalmology by Dr. May. The material included agrees with the thinking of modern otolaryngologists and truly reflects the lengthening shadow of a great teacher, Dr. Henry L. Williams, of the Mayo Clinic. The three former fellows of the Mayo Clinic have dedicated this volume to their teacher and friend, and its composition is such that he might well be proud of it.

Das Röntgenschichtbild des Ohres. The Tomogram of the Ear. By Prof. Karl Mündnich and Dr. Kurt-Walter Frey. With introduction by Prof. Dr. A. Herrmann and Prof. Dr. H. v. Braunbehrens. Archiv und Atlas der normalen und pathologischen Anatomie in typischen Röntgenbildern. Band 83, Ergänzungsbände, Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin: Diagnostik, Physik, Biologie, Therapie. Herausgeber: R. Glauner et al. [In German and English.] Cloth. 66 marks; $18.75. Pp. 123, with 205 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

This profusely illustrated book represents a great deal of work on the part of the authors. Each illustration is accompanied by an easily understandable line drawing labeled in detail. The text is in both German and English in parallel columns. The engraving of the illustrations occasionally leaves something to be desired. The world literature on tomography of the temporal bone is reviewed, and the authors describe their own techniques in detail. Hypoclinoid blurring has been produced by the Massiot "Polytome." Methods are presented for taking 1-mm. sections through the temporal bone in six different positions. The normal anatomy of the temporal bone is depicted in 62 illustrations. The remaining films demonstrate a wide variety of lesions, including atresias, fractures, infections, and tumors.

The authors' introduction correctly states that tomography is to be considered an amplification of, not a substitute for, conventional mastoid films taken with good technique in properly chosen positions. Certain lesions, however, especially labyrinthine fistulas and severe congenital atresias, can be examined effectively by the tomographic technique. Although this book may not be of great interest to either the general radiologist or the surgically oriented otologist, it is recommended strongly to those roentgenologists particularly interested in the radiologic examination of the temporal bone.

Röntgendiagnostik des Magen-Darmkanals. Von Prof. Dr. R. Prévôt und Priv.-doz. Dr. M. A. Lassrich. Cloth. 119 marks; $28.30. Pp. 346, with 544 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart, West Germany; [Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16], 1959.

It is difficult to review in a comprehensive way the roentgenographic diagnosis of diseases of the gastrointestinal tract, gallbladder, and pancreas. The authors have succeeded admirably in their presentation of this material, avoiding both redundancy and repetition. A wealth of material has been compiled in about 300 pages. The text is adequately and beautifully amplified by the illustrations. It is refreshing to note the emphasis placed on differential diagnosis. The text includes scholarly discussions of such subjects as congenital anomalies, inflammatory and neoplastic diseases, functional disturbances, and localization of foreign bodies. The anatomic and pathological changes associated with each of the conditions have not been overlooked. For particular commendation were the references made to the acute abdomen, especially in the pediatric patients. The "scout film," mucosal pattern demonstrations, and the more recent advances in intravenous cholangiography, as well as their limitations, are here discussed. Brief historical references and a well-documented bibliography round out the volume. This book can be recommended unreservedly not only to radiologists but to any specialist or practitioner who is interested in the roentgenographic diagnosis of gastrointestinal disorders. A good reading knowledge of German is desirable.

QUESTIONS AND ANSWERS

ADVERSE DRUG REACTIONS AND MALPRACTICE

To THE EDITOR:—*Would a physician be liable for malpractice if a patient had an adverse reaction to a drug in a case in which there was no history of previous intake of or reaction to the medicament?*

M.D., Illinois.

ANSWER.—Adverse reactions to drugs are of two major categories, toxic or allergic. Patients whose tolerance to the pharmacological action of the drug is low may have exaggerated and alarming responses to ordinary moderate doses of the drug. Side-effects unrelated to the drug's therapeutic action are considered toxic effects, such as sedation from antihistamines or overstimulation from epinephrine. Allergic reactions to drugs have no pharmacological basis and are manifestations of altered tissue responses. Urticaria, asthma, anaphylaxis, "serum sickness," thrombocytopenia, and granulocytopenia are examples.

The fact that a patient has a low tolerance can be ascertained only when there is a history of previous reaction from that class of drugs, but administration of normal doses to this type of patient usually causes unpleasant but not serious effects. In a case in which disastrous side-reactions may ensue, it is wise to give a preliminary small dose before the therapeutic dose is given. Whether failure to do this would be considered malpractice or not is questionable and would also depend on the usual custom in the community. The causing of side-effects from approved drugs is usually not a basis for a malpractice suit, unless the physician has been careless in supervising the treatment and observing the patient. For example, undesirable effects may be produced by corticosteroid therapy, but the doctor and the patient must be aware that the side-effects may develop in the patient during this type of treatment for asthma or rheumatoid arthritis. If serious side-effects arise because the drugs are used indiscriminately and without medical supervision, negligence can be claimed. The physician assumes added responsibility when administering new drugs not yet approved for general use.

Generally, the physician cannot be blamed for the allergic effects of a drug if he has avoided the use of potent allergenic drugs, when these were not necessary; inquired about the patient's previous response to the particular drug; made skin tests, where these were applicable; and made preliminary use of a fraction of the dose, when doubt existed. A skin test result is not always dependable, since it may be negative in the presence of allergy. The physician may be held negligent if he bases his opinion of the drug's harmlessness on such negative skin test results. Certain drugs will produce positive results of skin tests and forebode the possibility of the sudden appearance of urticaria, asthma, or anaphylaxis, and some of the most used drugs in this category are penicillin, streptomycin, animal serums, organ extracts (insulin, liver fractions, and pituitary products, including ACTH), enzymes, and other organic and some inorganic preparations. The physician is responsible for knowing this list. The result of a skin test with penicillin or serum is significant only to screen the patients prone to immediate (anaphylactic) reaction, which has no relation to delayed "serum sickness." Malpractice is established on proof of negligence, which is determined by the usual practice among physicians. For example, serum injections are rarely administered without a previous test, and, as the population becomes increasingly sensitive to penicillin, the custom of preliminary skin-testing should become more routine; when it does, failure to make preliminary skin tests may be regarded as negligence.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

TREATMENT FOR TAPEWORMS

To THE EDITOR:—*What is the treatment for a patient infested with Taenia saginata? Quinacrine has been used, but apparently the head remains.*

Lloyd H. Murdock, M. D., Zwolle, La.

ANSWER.—Of the many anthelmintics that have been used to rid a patient of T. saginata quinacrine is the most effective and least toxic. Failure to obtain the head is most often due to inadequate preparation of the patient's intestinal tract before the anthelmintic is given; the fact that the drug is impotent or not fresh, especially when oleoresin of aspidium is used; and the lack of intelligent cooperation by the patient.

The following routine should be used. 1. For two days before treatment the patient should adhere to a light, residue-free diet. 2. The night before treatment the patient takes 1 tbsp. of a saline purge such as sodium sulfate dissolved in a full glass of water. 3. On the day of treatment the patient is kept in bed and receives no breakfast except plain tea or black coffee; 30 mg. of phenobarbital is given one hour before treatment. 4. One hour later the patient receives 0.2 Gm. of quinacrine. Depending on the

weight of the patient the same dose is repeated every 10 minutes for four or five doses, until a total of 0.8 to 1.0 Gm. has been given; 0.6 Gm. of sodium bicarbonate is given with each dose of quinacrine to allay nausea. 5. Two hours after the last dose of quinacrine the saline purge is repeated. 6. Save all stools. It is best to collect them in a commode filled with warm isotonic sodium chloride solution, with the patient's anus immersed in the solution so that the worm is passed from the body to the solution, because the cooling and drying effects of the air may cause the worm to break in the region of the slender neck. If the head is retained it will mature in two or three months and the patient will start to pass segments and ova again. 7. Examine all stools. Usually the entire worm, 5 to 25 meters in length and stained deep yellow by the medicament, is passed at one time. Examine the worm. As the head is approached the worm becomes narrower and is thread-like in the region of the neck. The head is wider than the neck, rhomboidal in shape, and usually black. 8. The patient may take food after a copious bowel movement results from the second purge.

When these directions are followed the rate of cure is high. T. saginata infestation is usually single but may be multiple. Man is the definitive host. The adult worm matures and lives in the intestinal tract of man, and proglottids and ova are passed in his stools. The larval stage does not occur in man.

ECLAMPTIC TOXEMIA

To the Editor:—*Please discuss the use of muscle relaxant drugs, particularly succinylcholine, for management of a patient with eclampsia. Would they be more effective than administration of hypertonic solutions of magnesium sulfate or barbiturates in this respect? What is the status of the antihypertensive drugs such as reserpine for control of hypertension in eclampsia? Which anesthetic agent should be given the eclamptic woman during delivery of a viable fetus?*

William S. Skanyd, M.D., Parma, Ohio.

Answer.—The administration of curare alkaloids and the synthetic curaremimetic drug succinylcholine is rarely justified in the management of a patient with eclampsia because of the hazard inherent in their use. The muscle components of eclamptic seizures can be alleviated by these agents, but they do not alter the basic abnormalities peculiar to this entity. The margin of safety between therapeutic doses and amounts which will produce diaphragmatic paralysis and hypoxia is narrow. This limits administration of them to physicians who are acquainted with their pharmacological properties and who have the training and facilities for artificial resuscitation by means of endotracheal intubation and continuous positive-pressure respiration. The combined use of magnesium sulfate, antihypertensive drugs, and barbiturates rarely fails to control eclamptic seizures. These drugs have wide margins of safety and are the preferred agents for the management of patients with eclampsia.

A combination of parenterally administered reserpine and hydralazine hydrochloride, which may be supplemented by one of the veratrum alkaloids, is indicated in the management of patients with eclampsia. These agents give effective management of the hypertensive crises and prophylaxis of cerebrovascular accidents which may occur. The antihypertensive drugs are not substitutes for the anticonvulsive action of magnesium sulfate. Many factors influence the choice of anesthesia for a given eclamptic patient. A pudendal block with procaine for vaginal delivery and local infiltration for abdominal delivery afford the smallest risk.

QUADRIPLEGIA AND MEDICAL TRAINING

To the Editor:—*A student suffered a spinal cord injury at the level of the sixth cervical vertebra during the last part of the sophomore year of medical school. He has fair elbow flexion, slight elbow extension bilaterally, and no hand function. Touch perception is present in the skin out to the wrists and in the right thumb. What degree of disability can a student have and still anticipate the completion of medical training?*

Russell E. Youngberg, M. D.
Loma Linda, Calif.

Answer.—The prognosis in quadriplegia due to cervical cord injury has changed radically in the past few years. Antibiotics, proper urologic care, and the tilt board for postural management have given adequate medical control of the patients, and with modern self-help devices such patients are able to eat, dress, groom themselves, keep clean, and use an electric typewriter, telephone, or tape recorder. Many quadriplegics have been in competitive business for years. A sophomore medical student should be able to finish schooling if family, fellow students, and faculty cooperate. He should plan to work in some phase of medicine not requiring hand function such as psychiatry, administrative medicine, or medical rehabilitation. Paraplegic and quadriplegic physicians are successfully carrying on active practices today. During consideration of this problem it is fundamental that ability as well as disability be taken into account.

BLOOD FROM CADAVERS

To the Editor:—*Has cadaver blood, such as has been used in Russia, ever been considered an acceptable source of blood in America? This question is often asked when blood centers have difficulty in getting sufficient donors.*

H. W. Garton, M. D., Fort Wayne, Ind.

Answer.—Cadaver blood for transfusion purposes attracted some attention in this country (Yudin, S.S.: Transfusion of Cadaver Blood, *J. A. M. A.*

106:997-999 [March 21] 1936) but has never gained acceptance. Objections to its use are (1) a preference for blood from the living donor rather than from the cadaver; (2) the legality of invasion of the body; (3) the difficulties of avoiding bacterial contamination of the cadaver blood (the procedure was restricted, by the Russians, to blood collected within six hours after death and to cadavers of those dying of emergency conditions such as coronary occlusion, cerebral vascular accidents, and severe trauma, since it was believed that such restrictions decreased or avoided the hazard of bacterial contamination); (4) the uncertainty of supply because of (3); (5) the need for stand-by facilities and personnel to collect the blood from suitable and available cadavers; (6) the greater convenience of live donors; and (7) the availability of a history of previous good health from the live donor, serving to protect the recipient. Energies devoted to blood procurement are best applied to the mobilization of living donors. Most treatises on blood procurement ignore the cadaver as a source of blood or merely mention it for historical interest.

WATER SOFTENERS AND LOW-SODIUM DIET

To the Editor:—*Does replacement of the calcium and magnesium ions by the sodium ion take place during the chemical process of softening hard water? Would this be a source of sodium to be calculated when placing a hypertensive patient on a low-sodium diet?*

M. D., Illinois.

Answer.—In some areas water contains in its natural composition sodium chloride in excess of the desired amount for hypertensive patients. The content of sodium in artificially softened water depends on the method of softening used. Large municipalities use the soda-lime type or some modification thereof, and the water is substantially free of sodium. Water treated to "zero" softness is unpalatable, and to overcome this natural water is often added. Smaller city and home units use a method of water softening predicated on ion-exchange. This water has a substantial sodium content, and the harder the natural water the higher the sodium content.

Laubusch and McCammon (*Am. J. Pub. Health* 45:1337 [Oct.] 1955) concluded that water softened by the ion-exchange (zeolite) method might contain more sodium than is desirable for some hypertensive patients. They gave as an example water with an initial sodium content of 387 ppm and a hardness of 1,250 ppm of calcium carbonate; after the cation-exchange process each liter would contain about 960 mg. of sodium (2.44 Gm. of sodium chloride). They stated, "Each situation must be considered individually. Ion-exchange or excess lime soda softening, even of very hard waters having a high initial saline content, would rarely be in any way physiologically harmful to a person in normal health. Except in those cases where the concentration of sodium, as well as of calcium and magnesium ions, in the presoftened water is unusually high, the effects of the additional source of sodium are not insurmountable for ambulatory patients on a less intensive sodium restriction regimen, provided that they are aware of the situation, its significance, its effects, and what might be done to overcome it."

VACCINATION REACTION

To the Editor:—*A one-year-old infant was given typhoid vaccine at the time a smallpox vaccination pustule was forming. He developed fever and convulsions. Can it be assumed that this was due to the concurrent administration of the vaccines? The patient, now aged 3, will be going to Europe next year and needs typhoid immunization. Would you advise the administration of fractionated doses of typhoid vaccine?*

John O. Martin, M.D., Falls Church, Va.

Answer.—It is difficult to determine whether the high temperature was due to the stage of the smallpox vaccination or whether it was precipitated by the typhoid vaccine. It would have been more prudent to have delayed typhoid vaccination until the active stage of the first vaccination had subsided. The dose of the typhoid vaccine (not stated) and the infant's central nervous status, i. e., whether he had cerebral palsy or a tendency to febrile convulsions, are important factors to consider. Since this patient received his basic typhoid immunization at infancy and is now 3 years of age, a "booster" dose of 0.1 cc. of typhoid vaccine administered intradermally should be sufficient. If the attending physician considers that a larger amount is necessary, then fractionated doses of the vaccine are indicated. (See "Report of the Committee on the Control of Infectious Diseases," published by the American Academy of Pediatrics, 1801 Hinman Ave., Evanston, Ill.)

HYPERGLYCEMIA AND NO GLYCOSURIA

To the Editor:—*How is it possible for a patient to have a blood sugar level of 525 mg.% and no glycosuria, with the specimens having been taken at the same time? The urine was collected by an indwelling catheter. The patient's nonprotein nitrogen level was 110 mg. per 100 ml. The urinary output was below normal.*

E. N. Krueger, M. D., Appleton, Wis.

Answer.—The renal threshold for glucose excretion may be elevated by renal disease, and this possibility is suggested by the increased level of nonprotein nitrogen reported. Glucose excreted in urine depends on the amount of glucose filtered from the blood by the glomeruli and the amount reabsorbed in the renal tubules. Diseases that damage the glomeruli, such as nephrosclerosis or glom-

erulosclerosis, will decrease or stop glomerular filtration of glucose from the blood, thereby causing hyperglycemia and no glycosuria. When anuria is present, regardless of the cause, much time may elapse before glucose equilibrium is established between the blood and the urine. The blood flow to the kidney is so decreased that the small amount of glucose filtered by the glomeruli is completely reabsorbed by the tubules. Urinary output of less than 400 cc. per day is usually accompanied by high blood sugar levels and little or no sugar in the urine.

In pyelonephritis the tubules are so damaged that glucose reabsorbtion decreases and there is a decrease of blood sugar content. If there is disease of the kidneys one should not depend entirely on the urinary sugar content to indicate the effectiveness of treatment.

PHOTOGRAPHY IN SURGICAL SUITES

To the Editor:—*Is there an ether explosion hazard if photographs are taken in an operating room with use of the available light, a Nikon camera, and high-speed Ektachrome film?*

F. Goldwasser, M.D., Alma, Ga.

Answer.—The Nikon camera and high-speed Ektachrome film used in conjunction with light from surgical lamps and other available room illumination is a nonhazardous method of photography in an operating room. If additional illumination is provided by customary flood lamps or photoflash lights, the bulbs and the power source must be at least 5 ft. above the floor and 3 ft. away from the anesthesia equipment to avoid the possibility of fire from flammable anesthetics.

POLIOMYELITIS VACCINE AND TONSILLECTOMY

To the Editor:—*It has been the practice not to perform tonsillectomies and adenoidectomies during July, August, and September because of the possibility of these patients' developing poliomyelitis. Has the poliomyelitis vaccine altered this situation?*

Donald I. Dean, M.D., Rushville, Ind.

Answer.—The Expert Committee on Poliomyelitis of the World Health Organization considered this problem and concluded that, since the vaccine has no appreciable influence on the excretion of poliovirus in the stool, and since there may be no interference with the growth of the virus in the pharynx, it is advisable to discontinue such elective procedures during the poliomyelitis season. More recently eight prominent virologists expressed a similar opinion. During 1958 in the United States 322 paralytic cases of poliomyelitis and 20 deaths were reported in persons who had received three injections of vaccine. These figures support the recommendation that elective tonsillectomies or adenoidectomies, or both, be postponed during the months when the incidence of poliomyelitis is high. See also "Editor's Column," *Journal of Pediatrics*, May, 1959.

LACTATION DUE TO HYSTERECTOMY

To the Editor:—*Is lactation a common occurrence after a hysterectomy has been performed? Is it of any significance? Is there an etiological relationship?*

Harry L. Clark, M.D., Brooklyn, N. Y.

Answer.—This consultant has heard of lactation taking place after hysterectomy, but such claims have not been validated nor has information about associated procedures that may have been done at same time, such as oophorectomy, been available. Nothing, other than stress, that might influence the factors initiating and maintaining lactation is associated with the operation. The endometrium and the myometrium are influenced by progesterone and estrogen and in turn might influence their utilization, but there is no known relationship between this and the removal of the uterus that might initiate lactation. In answer, it is correct to make the dogmatic statement that lactation is not commonly observed to take place in a woman after a hysterectomy.

SCHICK TEST—DTP—DTPP

To the Editor:—*Should a child who has never received immunization for diphtheria and has a negative response to the Schick test receive three injections of diphtheria toxoid, or will it suffice to give a booster dose?*

Abraham Katz, M.D., Bronx, N. Y.

Answer.—The child who has not received immunization for diphtheria and who shows a negative response to the Schick test should be retested with fresh Schick test material. If the test result remains negative, diphtheria toxoid need not be administered. Most authorities state that such a person has acquired adequate immunity without the primary series of toxoid injection. These persons usually live in congested urban areas, have been exposed to others with subclinical infections of diphtheria, and contact the bacillus in doses too small to cause the disease yet adequate to elicit a protective antibody response.

Triple antigen—a mixture of diphtheria and tetanus toxoids and pertussis vaccine (DTP)—has been widely used in the United States since 1943. Three properly spaced doses of the adjuvant-containing antigen, administered intramuscularly, should protect simultaneously against these three diseases. Zoeller of the Paris Pasteur Institute (C. Zoeller, Bacille diphthérique, in Natan-Larrier, L.: Traité de Microbiologie, Paris, Gaston Doin & Cie, vol. 2, p. 88, 1934) gave evidence that higher and more lasting immunity responses result when toxoid doses are administered farther apart—preferably

at four-week to six-week intervals. A booster dose of DTP is advised two or three years later and should be repeated when the child enters school. Reactions are mild when aluminum phosphate is used as an adjuvant. The National Institutes of Health recently released quadruple antigen against diphtheria, tetanus, pertussis, and poliomyelitis (DTPP). Two reputable commercial biological laboratories market it. A periodic booster dose is advised. Local reactions are infrequent and transient. Such systemic reactions as fever occur somewhat more frequently than after administration of DTP, occasionally exceeding 103 F (39.4 C) rectally but usually dropping to normal within 24 to 36 hours, especially after administration of a few doses of aspirin and liberal quantities of water by mouth. Quadruple antigen (DTPP) is not recommended for use in patients over the age of 6 or 7 years, but it confers protection against these four diseases at the earliest age, if started at 3 months of age and administered as directed.

TETANUS TREATMENT AND PROPHYLAXIS

To the Editor:—*In* The Journal, *Aug. 15, page 2036, a sensitivity test involving the intravenous use of tetanus antitoxin is recommended as being safe. This test is new to us, and, since we occasionally receive inquiries from physicians about sensitivity tests for our tetanus antitoxin, we would appreciate information or references on the test.*

Hugh Macdonald, M.D.
Lederle Laboratories
Pearl River, N. Y.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*In the past 35 years, in the Communicable Disease Service, over 26,000 patients with diptheria, 400 to 500 with tetanus, and many with meningococcus meningitis and other diseases requiring serum or antitoxin treatment were cared for prior to the advent of antibiotics. Some time ago the following rules were given about the use of antitoxins and serums.*

Before either is administrated to a patient, a skin test and a control are done and their results compared in 30 minutes. If the result is positive, desensitization is required before the patient receives the serum under test. A negative skin test result is not considered evidence for lack of systemic sensitivity, and the intravenous test is next applied.

The intravenous test is made in the following manner. The patient's blood pressure is taken and recorded; 0.1 cc. of the antitoxin or other serum in question is diluted in 10 cc. of isotonic sodium chloride solution and injected slowly into the patient's vein within 5 minutes; and the patient's blood pressure is then taken and recorded every 5 minutes for 30 minutes. If the blood pressure falls 20 points or more, it is considered best to desensitize the patient before the serum is administered. This method has been changed a little from the original test, but years of experience have shown it to be the safest.

Time is often an essential factor in treating the patient. Should a patient be highly sensitive to tetanus or diphtheria antitoxin, the usual method of desensitizing (repeated administration of small doses at frequent intervals) may be too time-consuming. Intravenous administration of heparin, 20 mg. per kilogram of body weight, will prevent serum reaction and anaphylaxis. It may take up to 18 days for complete elimination of foreign proteins (of antitoxins) from the blood stream; therefore, it is necessary to keep the patients heparinized during that time.

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TETANUS IMMUNE GLOBULIN

To the Editor:—*In* The Journal, *Sept. 5, page 130, a tetanus immune globulin biological substance is referred to. Is this the pooled gamma globulin ordinarily used for the prophylaxis of measles and poliomyelitis or is it a separate biological product?*

Jerome Glaser, M.D.
85 San Gabriel Dr.
Rochester, N. Y.

The above comment was referred to the consultant who answered the original question, and his reply follows.—Ed.

To the Editor:—*Tetanus immune globulin is made by Cutter Laboratories of Berkeley, Calif., distributed with the trade name of "Hyper-Tet," and available in California only. It is packaged in 1,500-unit vials for administration by intramuscular injection. Tetanus immune globulin consists of the gamma globulin fraction prepared from venous blood of persons who have been immunized with tetanus toxoid. Administration of it is restricted to patients who are allergic to horse serum and in whom the prophylactic immunizing injection of horse serum tetanus antitoxin might produce an untoward allergic reaction. Pooled gamma globulin, which is used in prophylaxis of measles or poliomyelitis, is not satisfactory, because the antitoxin content is low and insufficient for adequate prophylaxis against possible tetanus infection.*